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SURVEY OF RECENT RESEARCH

NUMBER TWO

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Survey of Recent Research

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Issued February 1984

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
Center for Prevention Services
Division of Immunization
Atlanta, Georgia 30333

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CONTENTS

INTRODUCTION 1

MEASLES

General 3
Clinical and Laboratory 4
Epidemiology 6
Prevention and Control 7
Selected Bibliography 13

RUBELLA

General 21
Clinical and Laboratory 21
Epidemiology 24
Prevention and Control 24
Selected Bibliography 28

INFLUENZA

General 35
Clinical and Laboratory 35
Epidemiology 36
Prevention and Control 39
Selected Bibliography 42

DIPHTHERIA-PERTUSSIS-TETANUS

General 53
Diphtheria 54
Pertussis 56
Tetanus 59
Selected Bibliography 62

OTHER VACCINE-PREVENTABLE DISEASES

General 73
Cholera 74
Dental Caries 74
Haemophilus influenzae Infections 74
Malaria 74
Meningococcal Infections 75
Multiple Sclerosis 76
Mumps 77
Other Herpesvirus Infections 78
Pneumococcal Infections 79
Poliomyelitis 81
Rabies 84
Smallpox and Vaccinia 85
Subacute Sclerosing Panencephalitis 86
Tuberculosis 88
Varicella-Zoster Infections 89
Viral Hepatitis 92
Selected Bibliography 97

VACCINES, TOXOIDS, AND ANTIVIRAL AGENTS—GENERAL

Vaccines and Toxoids 137
Antiviral Agents 137
Selected Bibliography 139

IMMUNIZATION—GENERAL

General 143
Health Care Delivery 145
Government and Law 146
Selected Bibliography 147

INTRODUCTION

Immunization: Survey of Recent Research presents a survey of recently published periodical literature in the field of vaccine-preventable diseases. Abstracts of the most significant articles are included as well as selected bibliographies of various topics in this field. Inclusion of an article in this publication does not imply endorsement by the United States Public Health Service of the article or of commercial drugs, products, or other therapeutic modalities mentioned.

In compiling these abstracts and bibliographies, use is made of the National Library of Medicine's interactive retrieval service, MEDLARS II. Under this system, some 2,600 foreign and domestic biomedical periodicals are searched for material dealing with or related to immunization and vaccine-preventable diseases. A description of the search parameters is included on the next page.

For each citation generated by the search, a decision is made to abstract, place in the bibliography, or omit. Initial selection of articles to abstract, and review of the final manuscript is done by the Surveillance, Investigations, and Research Branch, Division of Immunization. Technical Information Services, Center for Prevention Services, writes original abstracts where required, compiles and edits the manuscript, and oversees publication and distribution.

Abbreviations of periodical titles are those used by MEDLARS II, and listed in the National Library of Medicine's *List of Journals Indexed in Index Medicus.* The journals in which articles originally appeared should be checked for reprint addresses.

This publication is the second in a series, the first issue of which appeared in April 1983. Citations of nearly all of the periodical literature published in 1982 on the subjects of immunization and vaccine-preventable diseases have been reviewed for this issue.

Questions or comments concerning this publication are welcomed and should be directed to:

Technical Information Services
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Search Parameters

Searches of the National Library of Medicine's databanks are restricted to those articles dealing with human subjects and having one of the following terms as a major or minor descriptor:

amantadine
antiviral agents
bacterial vaccines
BCG vaccine
brucella vaccine
bulbar poliomyelitis
chickenpox
cholera vaccine
cytarabine
diphtheria
diphtheria toxoid
encephalitis, post-vaccinal
fungal vaccines
immunization
immunization, passive
immunization schedule
immunization, secondary
influenza
influenza vaccine
measles
measles vaccine
mumps
mumps vaccine
pertussis vaccine
plague vaccine
poliomyelitis
poliovirus vaccine
poliovirus vaccine, oral
rabies vaccine
ribavirin
rickettsial vaccines
rubella
rubella vaccine
smallpox
smallpox vaccine
staphylococcal toxoid
staphylococcal vaccines
subacute sclerosing panencephalitis
tetanus
tetanus toxoid
toxoids
typhoid-paratyphoid vaccines
vaccines
vaccines, attentuated
vaccinia
vaccination
viral vaccines
whooping cough

MEASLES

General

Progress in Measles Elimination

A.R. Hinman, D.L. Eddins, C.D, Kirby, W.A. Orenstein, R.H. Bernier, P.M. Turner, Jr. and A.B. Bloch. JAMA 1982 Mar 19;247(11):1592-5.

In October 1978, encouraged by the impressive initial gains made in the childhood immunization initiative, Secretary Califano announced a new initiative: the elimination of indigenous measles from the United States by October 1, 1982. Record low levels of reported measles occurred in 1979 and 1980. For the first 39 weeks of 1981, there were 2,668 cases of measles reported in the United States. This represents a 79% decrease from the 12,918 cases in the comparable period in 1980. During this same period, more than 90% of the nation's counties were free of measles, and only 86 counties (2.7%) had reported measles more than twice during the year. This indicates that the vast majority of the nation is free of indigeous transmission of measles at present.

To date, there has been little indication that the rate of primary vaccine failures (5% to 8%) is adequate to permit sustained transmission of of measles when it is introduced to a previously measles-free area. An average of two importations has been occurring per week. Most importations have resulted in no secondary spread. However, importations will continue to occur even after indigenous transmission is interrupted.

Record high immunization levels have been attained in the nation's children, and effective surveillance and response measures are in place throughout the country. Achievement of the national target of measles elimination by October 1982 appears feasible, provided the current level of effort can be maintained.

Experience with Measles in Canada and the United States

J.W. Davies, S.E. Acres and P.V. Varughese. Can Med Assoc J 1982 Jan 15;126(2):123-5.

Authors' abstract: The United States is attempting to eliminate indigenous measles by October 1982. Progress in this effort appears to be related largely to the fact that all children must now be vaccinated before starting school and that unvaccinated children are not allowed to attend school during epidemics. Canada has not yet made a similar concerted effort to eliminate measles. The epidemiologic features of the disease in Canada and the United States have generally been similar, but some differences have emerged in recent years: Canadian rates are currently about 10 times higher, and the highest incidence in Canada is still in children 5 to 9 years of age, whereas in the United States the highest incidence is now in children aged 10 to 14 years, the result of intensive vaccination programs for preschool and early school-aged children.

Measles and Rubella in Adolescents and Young Adults

A.R. Hinman. Hosp Pract 1982 Oct;17(10):137-46.

Author's abstract: Measles and rubella have declined dramatically since 1979, yet both occur much more frequently than expected among persons of high school and college age. Over the past two decades, changes in the epidemiologic characteristics of these diseases have posed the most serious impediment to eradication. Approaches to identification and immunization of susceptible individuals are evaluated.

Measles. The GP View

J.G. Munro. Aust Fam Physician 1982 Mar;11(3): 153-5, 157.

Journal abstract: Measles is still a common disease in Australia and causes significant morbidity both in itself and in its complications. Dr. Clarke Munro discusses the clinical features and management. Although measles can now be prevented by vaccination, immunization rates remain disappointingly low.

Measles and Measles Vaccine in Isolated Amerindian Tribes. I. The 1971 Trio (Tiriyo) Epidemic

J. van Mazijk, F.P. Pinheiro and F.L. Black. Trop Geogr Med 1982 Mar;34(1):3-6.

Authors' abstract: Measles in an unvaccinated virgin population exacted a death toll of 4.2% which fell particularly hard on the age groups which would ordinarily be protected by maternal antibody. The organ system most affected was quite variable. When the virus spread to a largely vaccinated village it caused only one death. Herd immunity seemed to protect many who were not vaccinated. Vaccine failed to protect 7.7% of the recipients. Some of these failures may have been due to erroneous records or vaccination in the presence of maternal antibody or inactivated vaccine, but most occurred in a few family groups related by genetics and similar past immunological experience.

Levamisole Therapy in Children at Risk from Severe Measles

A.G. Wesley, H.M. Coovadia and P. Kiepiela. Ann Trop Paediatr 1982 Mar;2(1):23-9.

Authors' abstract: A placebo-controlled trial of Levamisole in 47 black children with measles is reported. The children were of satisfactory nutrition but at risk from severe disease as judged by a lymphopenia of less than 2000/mm^3 early in the exanthem. A placebo or Levamisole (2.5 mg/kg/dose) was given orally weekly for six weeks. Death or persistence of radiological pneumonia at six weeks occurred in 74% of the Levamisole and 92% of the placebo group. No side effects of the drug were noted. The immune responses that were monitored for six weeks were total lymphocyte and lymphocyte subpopulation counts, PHA stimulated lymphocyte transformation, leukocyte migration inhibition, measles antibody titers and serum levels of immunoglobulins and complement components. In none of these was a significant difference found between the two groups. While there was a trend clinically towards complete recovery in the group that received Levamisole, statistically it was not significant, and therefore Levamisole cannot be recommended for treatment of measles.

Clinical and Laboratory

Atypical Measles Syndrome: Pathologic and Serologic Findings

D. Annunziato, M.H. Kaplan, W.W. Hall, H. Ichinose, J.H. Lin, D. Balsam and V.S. Paladino. Pediatrics 1982 Aug;70(2):203-9.

Authors' abstract: The clinical course of measles occurring in 17 adolescents who had previously received killed measles vaccine is described. All adolescents had a peripheral dermatitis. Fifteen had characteristic pulmonary infiltrates. Serologic study in six adolescents using immunoprecipitation of 35S-methionine-labeled measles virus antigens revealed that 5/6 acute sera lacked antibody to the hemolysin antigen whereas 5/6 sera contained antibody to hemagglutinin antigen. Skin biopsies, obtained from three patients, demonstrate a combination of an Arthus reaction and delayed hypersensitivity. The typical measles histologic complex was absent. Measles virions were seen in the deep dermal blood vessels. The serologic and histopathologic presentation of this disease indicates that killed vaccine does not adequately induce antibody to the hemolysin (F) which is necessary to prevent cell-to-cell spread of paramyxoviruses. Killed vaccine does, however, produce hemagglutinin antibody and simultaneously incites later hypersensitivity to wild virus infection, producing the unusual dermatopathologic reaction seen.

Measles Encephalitis. Clinical, EEG, and Psychometric Aspects at Follow-Up (Italian)

P.A. Battistella, G. Meneghetti, F. Turcato and P. Cadrobbi. Riv Patol Nerv Ment 1981 Mar-Apr;102(2):69-77.

English summary: A follow-up of 23 patients with measles encephalitis was carried out six months to ten years after the onset of the disease. Neurological and electroencephalographic features have been examined together with specific psychological tests. Clinical and electroencephalographic abnormalities, frequently observed during the acute phase of the disease, were rarely detected during the follow-up. However intellectual performances with specific visuo-spatial and attentional involvement are often impaired. Specific psychological tests are required to evaluate visuo-spatial and attention performances, frequently impaired as a consequence of the disease; these are often considered minor psychological disturbances as they are limited to scholastic performances. The authors conclude that, although measles encephalitis is a fairly serious illness during its acute phase, it tends to improve with time until recovery is complete. The psychological residual deficits, detected during the follow-up, should not be considered as minor disturbances.

A Study of Deafness in West Africa

C. Holborow, F. Martinson and N. Anger. Int J Pediatr Otorhinolaryngol 1982 Jun;4(2):107-32.

Authors' abstract: Some 800 profoundly deaf children from 4 Yoruba states in Nigeria were assessed and examined in an attempt to identify the causes of deafness in this part of West Africa. It was found that measles, meningitis and rubella were the three major preventable diseases causing deafness. Genetic abnormalities, in contradistinction to other tropical countries, do not seem to be very important and chronic ear infections show different manifestations in this area to the situation reported in East Africa. The overwhelming problems that face the deaf and any possible extension of services for the deaf are detailed. In view of these, it seems that the most cost-effective way of helping the deaf in Nigeria is by immunizing the population against those infectious diseases that cause the disability. This policy would accord with the recent initiatives by the United Nations: the International Year of the Child (I.Y.C.) and the International Year of the Disabled Person (I.Y.D.P.) as well as The Expanded Programme of Immunization (E.P.I.) of the World Health Organization.

Measles and Acute Glomerulonephritis

C.Y. Lin and H.C. Hsu. Pediatrics 1983 Mar;71(3):398-401.

Authors' abstract: A 5-year-old boy had transient glomerulonephritis following measles infection. Serologic studies at the early onset of the disease showed decrease of serum C3, C4, and Clq levels with normal serum properdin factor B. Renal glomerular histology revealed a mild acute proliferative glomerulonephritis. Measles virus antigen, C3, C4, and immunoglobulin G (IgG) were demonstrated in the glomerulus, suggesting an immune complex deposition. Ultrastructurally, subepithelial, intramembranous, and subendothelial electron-dense deposits were noted, suggesting a postinfectious immune complex glomerulonephritis. It is suggested that the measles virus antibody complexes are deposited in the glomerulus and activate the classic pathway of complement, leading to a self-limited glomerulonephritis.

Antibodies Against Measles Virus Polypeptides in Different Disease Conditions

E. Norrby, C. Orvell, B. Vandvik and J.D. Cherry. Infect Immun 1981 Dec;34(3):718-24.

Authors' abstract: The occurrence of antibodies to the nucleoprotein and matrix (M) antigens of measles virus was determined in early and late measles convalescent sera and in sera from patients with multiple sclerosis, subacute sclerosing panencephalitis, chronic active hepatitis, and atypical measles. Antibodies to the two components were identified separately in serially diluted samples both by radioimmune precipitation assays and by complement fixation tests employing purified nucleoprotein and M components as antigens. The antibody response to M antigen in connection with acute infections was weak, and with time titers of antibodies to M antigen were reduced below detectable levels in most cases. A different situation was seen in patients with atypical measles. A pronounced antibody response to M antigen was shown to be a part of the generally accentuated immune response in these patients. Confirming results of others, it was shown that in spite of the increased antibody titers against most measles components in sera from patients with subacute sclerosing panencephalitis, no or only low titers of antibodies to M antigen were present. However, a similar representation of antibodies to measles virus components was also seen in sera from patients with active chronic hepatitis. The significance of this finding for the interpretation of a weak antibody response to M antigen in the presence of a pronounced antibody response to other components is discussed.

T-Lymphocyte Subpopulations in Relation to Immunosuppression in Measles and Varicella

P. Arneborn and G. Biberfeld. Infect Immun 1983 Jan;39(1):29-37.

Authors' abstract: Patients with measles or varicella were studied during the acute phase (first week) of illness and, after recovery, by lymphocyte stimulation tests and determination of T-lymphocyte subpopulations, using the monoclonal antibodies Leu 2a and Leu 3a directed at the suppressor/cytotoxic and the helper T-cell subsets, respectively. Low proliferative responses to phytohemagglutinin were found during the acute phase of both diseases. The response to purified protein derivate of tuberculin was also low in all measles patients tested and in some of the varicella patients. In both infections increased spontaneous DNA synthesis was demonstrated. In the acute phase of measles there was T lymphocytopenia but no change of the ratio between T lymphocytes of helper and suppressor/cytotoxic cell phenotypes. In the acute phase of varicella the percentage and the absolute number of Leu 2-positive (suppressor/cytotoxic) T cells were increased. Measurement of the size of the lymphocytes indicated activation of this subset. Cryopreserved blood mononuclear cells from the acute phase of varicella could suppress the phytohemagglutinin response of autologous convalescent-phase cells. This was not seen when cells from measles patients were tested. The suppression of the lymphocyte stimulation response in varicella is probably in part caused by activation of suppressor cells, whereas the suppression of the stimulation response in measles seems to be due mainly to other mechanisms.

A Comparative Analysis of Measles Virus RNA by Oligonucleotide Fingerprinting

J.R. Stephenson and V. ter Meulen. Arch Virol 1982;71(4):279-90.

Authors' abstract: Isolates from two cases of acute measles, one case of acute measles encephalitis and three patients with subacute sclerosing panencephalitis were compared. This comparison was based upon the electrophoretic analysis of T1 oligonucleotides from single-stranded, full-length RNA isolated from cytoplasmic nucleocapsids. Although all viruses have oligonucleotides in common, each isolate generated a unique pattern of oligonucleotides. However, no group of oligonucleotides was observed which would allow a differentiation between viruses isolated from acute infections and those isolated from CNS diseases; indicating that probably all measles viruses differ in their nucleotide sequence, regardless of origin.

Radioimmunoassay for the Detection of Virus-Specific IgA Antibodies in Saliva

M.G. Friedman. J Immunol Methods 1982 Oct 29;54(2): 203-11.

Author's abstract: The use of a sensitive and versatile radioimmunoassay (RIA) for detection of mumps-specific IgA and measles-specific IgA in unconcentrated saliva samples is described. The samples were obtained either by expectoration or by swabbing of the oral cavity, with or without stimulation of secretion, and were inactivated and clarified before testing. Mumps-specific IgA antibodies were detected as early as one day after onset of illness and peaked at 1-2 weeks after onset. Measles-specific salivary IgA antibodies were detected in 15-month old children 2-3 weeks after immunization. These results suggest that the RIA technique may be useful for early diagnosis of viral infections and for confirmation of response to immunization without the need for a blood sample, as well as for the study of the secretory immune response in very young and older subjects.

Epidemiology

Epidemiological Models of Poliomyelitis and Measles and Their Application in the Planning of Immunization Programs

B. Cvjetanovic, B. Grab and H. Dixon. Bull WHO 1982;60(3):405-22.

Authors' abstract: This report describes the construction and application of epidemiological models of measles and poliomyelitis. In these models, epidemiological classes and their age structure have been based on the natural history of these diseases in the populations aged 0-19 years. The flow of the population through the classes has been expressed as an equation system suitable for computer interpretation. The models have been used to simulate both the natural course of the diseases and the effect of various immunization schemes. The models were also used to explore prospects for control and eradication of these diseases with specific immunization programs and their relative effectiveness and cost-effectiveness are discussed.

Imported Measles in the United States

R.W. Amler, A.B. Bloch, W.A. Orenstein, K.J. Bart, P.M. Turner, Jr. and A.R. Hinman. JAMA 1982 Nov 5;248(17):2129-33.

Authors' abstract: In the period 1980-1981, two hundred nine imported measles cases were reported in the United States. These cases represent 1.3% of the total of 16,630 cases of measles reported to the Centers for Disease Control (CDC) during that period. An average of two imported measles cases were reported each week. The travelers with imported measles were United States citizens and foreign nationals who arrived from 47 different countries throughout the world. However, returning United States citizens have accounted for a rising proportion of imported measles cases. Approximately half (49.3%) of the imported cases were reported by four areas: California, New York State exclusive of New York City, New York City, and Florida. Seven measles outbreaks occurring following importations during the two-year period were identified. In addition to 114 imported measles cases reported to the CDC in 1981, 437 measles cases were reported to be caused directly or indirectly by those importations. The actual number of import-associated cases may have been considerably higher. Imported measles and associated cases together accounted for at least 17% (551/3,124) of reported measles cases in 1981.

Hospitalizations for Measles, 1970-78

T.F. Nolan, Jr., R.A. Goodman, P.A. Patriarca and A.R. Hinman. Am J Public Health 1982 Sep;72(9):1037-9.

Authors' abstract: The National Hospital Discharge Survey of the National Center for Health Statistics was analyzed for measles hospitalizations. From 1970-1978 there were an estimated 52,301 hospitalizations for measles, or approximately 5,800 per year. The median patient age was three years, and the median length of stay was four days. Forty-one percent of the discharges listed respiratory complications, 10 percent listed otitis media, and 3 percent listed neurologic complications. Based on this analysis, hospitalizations for measles accounted for 314,063 hospital days during the period 1970-1978.

Synergistic Impact of Measles and Diarrhea on Nutrition and Mortality in Bangladesh

F.T. Koster, G.C. Curlin, K.M. Aziz and A. Hague. Bull WHO 1981;59(6):901-8.

Authors' abstract: The efficacy of recent efforts to improve the delivery of available vaccines, especially in the developing countries, can be aided by surveys that identify populations suffering from unduly high morbidity and mortality as a result of a particular disease. This paper gives the results of a prospective household surveillance of 5775 children in 12 villages in Bangladesh, in which the occurrence of measles and diarrhea, and changes in nutritional status, and the causes of all deaths during a 12-month period were monitored. The measles case-fatality rate was 3.7% among all children. Prolonged diarrhea was the most common complication in fatal cases. The greatest weight loss was seen in children with measles complicated by prolonged diarrhea, and children under 4 years of age in this group failed to achieve "catch-up" growth. Thus measles and diarrhea appeared to interact synergistically to increase mortality and the irreversible effects of nutritional deprivation. This information should provide further impetus to an extensive measles vaccination program in Bangladesh. Until then, nutrition intervention programs should be aimed at children under 4 years of age, convalescing from measles.

Measles in England and Wales—I: An Analysis of Factors Underlying Seasonal Patterns

P.E. Fine and J.A. Clarkson. Int J Epidemiol 1982 Mar;11(1):5-14.

Authors' abstract: Examination of the weekly measles notifications for England and Wales, 1950-1979, reveals a regular biennial pattern of major and minor epidemics before the national immunization program began in 1968, followed by an annual cycle of minor epidemics. Each year the reported incidence reaches its annual low between weeks 36 and 39, very close to the opening of primary schools. Analysis of these data with a simple mass action model reveals that the underlying transmission parameter has had a similar annual pattern in years of major and minor epidemics. The transmission parameter rises three times each year, coinciding with opening of school terms, and falls with school term and mid-term holidays. This pattern of the transmission parameter has been maintained in the decade since national vaccination began, indicating that the importance of schools in the annual dynamics of measles has not changed. The analysis further suggests that the national measles vaccination program has not lowered the total number of individuals susceptible to measles in England and Wales.

Measles in England and Wales—II: The Impact of the Measles Vaccination Program on the Distribution of Immunity in the Population

P.E. Fine and J.A. Clarkson. Int J Epidemiol 1982 Mar;11(1):15-25.

Authors' abstract: Measles notification and vaccination data for England and Wales are analyzed to reveal trends in age-specific incidence and immunity levels in successive cohorts born since 1950. A method for cumulating infection and vaccination experience is described in detail. The analysis reveals that there was a trend towards lower incidence rates of measles, and towards younger average age of cases, for the 10 years prior to commencement of the national immunization program in 1968. Since the immunization program began, there has been a dramatic and complicated shift in the age pattern of measles immunity in the population, such that some young age groups are now better protected, but some older age groups less well protected, than they were before the program. These trends are discussed with critical attention to the possibility that they may reflect biases in the available data. It is concluded that the number of susceptibles over 10 years of age is increasing, and that this could have appreciable public health implications in the years to come. It appears that the total number of individuals susceptible to measles has remained relatively constant, between 4 and 4.5 million, before and after the immunization program. Though consistent with basic theory, this maintenance of constant overall number of susceptibles has not been demonstrated before. Because the implications of these analyses are important for the strategy of measles control, it is important that appropriate serological surveys be carried out in order to assess the validity of the findings.

Prevention and Control

The Case for Global Measles Eradication

D.R. Hopkins, A.R. Hinman, J.P. Koplan and J.M. Lane. Lancet 1982 Jun 19;1(8286):1396-8.

Authors' abstract: The global eradication of measles is desirable because the disease occurs almost universally, affects large numbers of children, can cause serious complications, and is responsible for about 900,000 deaths a year in developing countries. The feasibility of a measles eradication program is suggested by the success of smallpox eradication, the availability of a heat-stable, cheap, and effective vaccine, and the fact that interruption of measles transmission has been achieved in some places. Eradication of measles globally would also result in the saving of the large sums of money being spent on measles treatment, vaccination, and surveillance.

The Global Elimination of Measles

W.H. Foege. Public Health Rep 1982 Sep-Oct; 97(5):402-5.

Author's introduction: Eric Hoffer, the American laborer-philosopher, once said, "Where there is the necessary technical skill to move mountains, there is no need for the faith that moves mountains." The technology for the global eradication of measles is at hand. What is needed is the social will to undertake such a breakthrough in international public health.

To assess the subject of global measles eradication, three questions must be answered: Can we eradicate measles? Should we eradicate measles? Will we eradicate measles?

The answer to the first question rests on scientific fact. We can eradicate measles. The smallpox eradication program proved that global eradication of certain infectious disease is possible. Although there are obvious differences, there are also epidemiologic similarities between measles and smallpox. They are both viruses that cause recognizable rashes, a characteristic which helps epidemiologic surveillance programs. They both confer lifelong immunity. Neither has an animal reservoir or inapparent chronic carrier state among human beings.

Since 1963, an effective and safe vaccine for measles has been available, and it has been widely used in the United States and other countries. In the past it has not received maximum use because it required a smoothly functioning cold chain of storage, transportation, and delivery to preserve the viability of the vaccine virus. There is now a more heat-stable vaccine that can remain potent in the freeze-dried state for 3 or 4 weeks at ambient tropical temperatures without refrigeration. The containers which maintain cold temperatures and protect vaccines have also been improved. Coupled with this technological progress is an economic advantage—the cost of measles vaccine has declined to the current World Health Organization (WHO) price of only 10 cents per dose in 20-dose vials.

Measles can be controlled through widespread and logical use of this vaccine.

World Eradication of Measles

A. R. Hinman. Rev Infect Dis 1982 Sep-Oct;4(5):933-9.

Author's abstract: From a theoretical and technical point of view, measles can be eradicated from the world. This disease has been eliminated for a period of years from at least one country in the developing world (The Gambia). Experience in the United States indicates that it will be eliminated from that country in the near future. Whether the necessary financial, political, and personnel resources to achieve global eradication can be mobilized in the next several years remains in doubt.

Measles and Rubella in the United States

H. W. Hethcote. Am J Epidemiol 1983 Jan;117(1):2-13.

Author's summary: The observed decreases in measles incidence in the United States have been due to both outbreak control and to increasing fractions vaccinated. Although outbreak control has helped to reduce the incidence and transmission of measles, complete and permanent eradication can only be obtained through herd immunity achieved by vaccination. Earlier calculations show that the fraction of children vaccinated must be very high for many years to achieve herd immunity for measles. Although current nationwide vaccination rates are close, they are not above the vaccination levels calculated to be necessary for herd immunity and the disappearance of measles. Of course, contact numbers and vaccination levels are not uniform throughout the U.S. so the some cities and states may now have local herd immunity.

In cities and states where herd immunity is particularly difficult to attain, the two-dose program, which involves a second dose of measles vaccine at school entry, could be used. Calculations show that herd immunity for measles is much easier to achieve with the two-dose strategy. As local heard immunity for measles in a community is approached, the frequency of outbreaks decreases. When local herd immunity is achieved, the vaccination program must be continued indefinitely with at least the same intensity to prevent outbreaks after imported cases. Measles could continue at low levels for many years in the U.S. before nationwide herd immunity and eradication are achieved.

Calculations show that the U.S. strategy of vaccinating young boys and girls against rubella is not as efficient as the British strategy of vaccinating only 11- to 14-year-old girls when the fraction immunized by vaccination is less than about 0.80; however, above 0.80, the U.S. strategy is better and can lead to eradication. Thus, the British strategy turns out to be the better strategy for Britain and for other countries where the fractions being immunized are below 0.80. The fraction of children in the U.S. being immunized against rubella by vaccination is now definitely above 0.80 so that the U.S. strategy is clearly the better strategy for the US.

According to calculations, herd immunity is much easier to achieve for rubella than for measles since the fractions vaccinated do not have to be as high. The current vaccination rates in the U.S. are above the levels calculated to be necessary for herd immunity and the disappearance of rubella; however, it is not clear when rubella will disappear since earlier vaccination rates were lower and the vaccination program was not started until 1969. The steady decrease in the number of reported cases of rubella in the U.S. may indicate that herd immunity and eradication will be achieved soon.

Assessment of Susceptibility to Measles and Rubella

S.R. Preblud, F. Gross, N.A. Halsey, A.R. Hinman, K.L. Herrmann and J.P. Koplan. JAMA 1982 Feb 26;247(8):1134-7.

Authors' abstract: We conducted a serological and questionnaire study of 755 U.S. Merchant Marine Academy cadets (aged 16 to 29 years) and their parents to determine the cadets' susceptibility rate to measles and rubella and to see if there was any difference in the accuracy of cadet and parental histories of previous infection and vaccination. Approximately 4% of the cadets were susceptible. We also determined the costs and the effectiveness of three alternative strategies for vaccinating susceptible adolescents and young adults: (1) vaccinating all persons regardless of past history; (2) serologically screening all persons and vaccinating only those who were susceptible; and (3) vaccinating all individuals who do not have physician-documented proof of proper vaccination, past infection (measles only), or serological immunity. The cost savings among the three alternatives are dependent on the proportion of potential vaccinees with records available for review and must be balanced against the proportion of susceptible persons protected by each alternative. We also found that a combined vaccination program for both measles and rubella is less costly than a program aimed at providing immunity to only one of the two diseases.

Measles in the Tropics and Public Health Practice

R. Davis. Trans R Soc Trop Med Hyg 1982;76(2): 268-75.

Author's abstract: Measles shows three distinct transmission patterns in the tropics, one each in urban, rural and insular or very remote areas. The characteristics of measles transmission are reviewed for each area, both with and without immunization. Planning must be based on the best use of currently underused infrastructure in the light of epidemiology. Mass mobile campaigns are not advised for urban areas. Vaccination of the sick and the well as part of episodic medical care is proposed, and vaccination of the sick is supported as safe and effective. Age floors and ceilings should be set with reference to the local situation; adoption of international "rules of thumb," without reference to local conditions, is inadvisable. A mixed strategy is urged for rural areas, with routine immunization against measles as part of a multi-antigen program. Routine immunization should be complemented by annual surveillance and containment during the seasonal trough. Research and development needs in measles control include better understanding of measles epidemiology, more operationally useful quantitative models, and trials of new control strategies. Control, elimination and eradication are defined and discussed.

The Role of Herd Immunity in Control of Measles

F.L. Black. Yale J Biol Med 1982 May-Aug;55(3-4): 351-60.

Author's abstract: Measles vaccine cannot give high seroconversion rates in developing countries. The high birth rates characteristic of these countries lead to infection at a very early age, thus making it difficult to vaccinate before exposure to the disease. Nevertheless, if given early in life, the vaccine can reduce the rate of virus circulation and thus raise the age at which children are infected. Once that is done, higher seroconversion rates can be obtained by raising the age at vaccination. During the period when vaccine is given at an early age, the titers in responding children will be low, and this will leave children of the next generation with little protection. It is important, therefore, that if vaccine is used early the program be intensively and consistently applied to control virus circulation before the next generation is born.

Economic Effectiveness of Using a Live Measles Vaccine in an Agricultural Area of the Ukrainian SSR (Russian)

N.A. Vasileva and V.N. Kashuba. Zh Mikrobiol Epidemiol Immunobiol 1982 Sep;(9):57-60.

English summary: Economic effectiveness of vaccination against measles in an agricultural region of the Ukrainian SSR has been studied. At the period preceding vaccination, expenses for each measles patient in the country were three times as low as those in towns. At the period of vaccination a considerable decrease in expenses covering the payment of sick-leave certificates given to mothers taking care of their sick children, in losses connected with absenteeism, in expenses for gamma globulin prophylaxis and the hospital treatment and outpatient servicing of measles patients was observed due to the sharp drop of the total morbidity rate and the increased number of schoolchildren among measles patients. In urban and rural areas the equalization of expenses for each patient occurred. In spite of increased expenses for each measles patient, a considerable economy of sums spent for controlling measles was achieved: about 70,000 rubles per annum.

An Investigation of the Causes of Failures in Measles Vaccination in Early Infancy

W. Shaoyuan, X. Xiuqing, Z. Yihao, S. Shuwang, L. Haijiang, L. Jingcai, H. Bincheng, X. Hongye and L. Tengxiao. J Biol Stand 1982 Jul;10(3):197-203.

Authors' abstract: Among 854 infants, residual maternal antibodies against measles virus were detected in 35% at the age of 4-5 months, in 16% at 6-7 months and in less than 10% at 8 months or older. At the various ages given above, the geometric mean titers (GMTs) of the maternal antibody in 82 seropositive infants were similar, about 1/5. After vaccination the seroconversion rates and the GMTs of 1070 seronegative susceptibles varied with their ages, being 64, 84, 94 and 96% in the 4-6, 7-8, 9-11 and 12 month groups respectively. Similar results were obtained with 82 infants bearing maternal antibodies, the rates of fourfold or greater antibody rise being 20% at 4-6 months, 45.8% at 7-8 months and 82.1% at 9-12 months. Thirty susceptibles who failed to respond to their primary vaccination before one year of age gave a 96.7% seroconversion when revaccinated after their first birthday. A one year follow up study showed that the younger the vaccinees were, the sooner the antibodies waned. It is suggested that young infants fail to respond to measles vaccination by reason of their immature immune response rather than by reason of interference by maternal antibody.

Methodologic Issues in the Evaluation of Vaccine Effectiveness: Measles Vaccine at 12 vs. 15 Months

J.S. Marks, G.F. Hayden and W.A. Orenstein. Am J Epidemiol 1982 Sep;116(3):510-23.

Authors' abstract: Initial studies of vaccine effectiveness are usually controlled clinical trials. Subsequent serologic and epidemiologic investigations cannot be as carefully controlled, and methodologic rigor must be considered when evaluating their results. The authors reviewed the methodologic features of greatest importance in the design of field investigations of vaccine efficacy and examined how different methodologic approaches may have influenced the results of studies of measles vaccine efficacy at 12 vs. 15 months of age. Among the serologic studies, time since vaccination was not controlled, so that children vaccinated several years ago at 12 months of age may have been compared with children vaccinated much more recently at later ages. Most studies included children vaccinated at several years of age as controls rather than children vaccinated only at the pivotal ages of 13-15 months. Finally, studies using a single clinic as their vaccine source found smaller differences in efficacy than studies using multiple vaccine sources, suggesting that variation in handling and storage may affect the results. Among the epidemiologic studies, no single methodologic feature clearly influenced whether there was significantly improved vaccine efficacy with increasing age at vaccination. However, studies differed with respect to intensity of effort to detect cases unreported through the usual channels; definition of what constituted a case of measles; whether the effect of mid-outbreak clinics on overall estimates of vaccine efficacy was considered; and inclusion of revaccinated children in the analysis. These methodologic variations can make it extremely difficult to evaluate the size and clinical importance of relatively small differences in vaccine efficacy. Greater attention to the methodologic features discussed here will be needed in future studies of vaccine efficacy.

Measles Immunity after Revaccination: Results in Children Vaccinated Before 10 Months of Age

C.C. Linnemann, Jr., M.S. Dine, G.A. Roselle and P.A. Askey. Pediatrics 1982 Mar;69(3):332-5.

Authors' abstract: Measles immunity was studied in children in a private pediatric practice who had been revaccinated because they had received their primary measles vaccination before 1 year of age. Antibody was measured in 72 of these children who had received the first injection of live measles virus vaccine at less than 10 months of age, and the second at greater than 1 year of age. Of the 72 children, 29 (40%) had no detectable antibody and the geometric mean titer for the group was approximately 1:4. Of the children with low antibody titers, 15 were given a third injection of measles vaccine and five (33%) still did not respond. Cell-mediated immunity as indicated by lymphocyte transformation to measles antigen was measured in 11 of the children. Five (45%) had responses to measles antigen, but the responses did not correlate with the presence or absence of antibody. This study confirms the observation that revaccination is unsuccessful in many children who received measles vaccine in the first year of life, and shows that even a third injection of vaccine may fail to produce a significant antibody response.

Reported Measles in Persons Immunologically Primed by Prior Vaccination

F.R. Smith, A. S. Curran, K.A. Raciti and F.L. Black. J Pediatr 1982 Sep;101(3):391-3.

From authors' discussion: In this study, 27% of the clinically diagnosed cases were not serologically characteristic of measles. The great reduction in number of measles cases has, presumably, left the absolute number of measleslike illnesses unchanged. As a result, these measles-mimicking diseases may now account for a substantial proportion of all reported measles cases. Alternatively, it is possible that customary serologic criteria, even broadly defined as in this paper, require modification to reflect an aberrant immunologic response in actual measles cases.

The fact that none of seven children, vaccinated at less than 15 months, produced anti-measles IgM, whether or not they were revaccinated, suggests that they had been sensitized by vaccine so that their response to re-exposure was modified. The observed secondary response supports previous studies which indicate that the capacity for anamnestic response is not always protective against measles infection. Furthermore, these data add weight to other evidence that booster immunization may not be effective in eliciting protective levels of immunity, and open to question the value of revaccination.

Further Field Testing of the More Heat-Stable Measles Vaccines in Cameroon

D.L. Heymann, E.L. Smith, J.H. Nakano, J.G. Jato, G.E. Maben and G.K. Martin. Br Med J [Clin Res] 1982 Aug 21;285(6341):531-3.

Authors' abstract: Two of the more heat-stable measles vaccines were field tested in Cameroon. Both maintained the minimum required infectivity titer and the ability to induce seroconversion after storage unreconstituted at 37° C for 14 days. One of the vaccines, studied after reconstitution, maintained its ability to induce seroconversion after reconstitution and storage at 25° C for 48 hours and at 37° C for at least four hours. The increased heat stability of the studied vaccines will not eliminate the need for a well-monitored system of vaccine conservation and distribution but will ease the rigid cold-storage requirements of conventional measles vaccines.

Application of Live Attenuated Measles and Mumps Vaccines in Children with Acute Leukemia

S. Torigoe, S. Hirai, K. Oitani, M. Ito, T. Ihara, T. Iwasa, H. Kamiya, M. Sakurai, S. Ueda and K. Yamanishi. Biken J 1981 Dec;24(4):147-51.

Authors' abstract: Eight children with acute leukemia in remission were immunized with live attenuated measles vaccine and 4 with mumps vaccine. Immunological examinations before vaccination showed that the numbers of white blood cells, percentages of lymphocytes, levels of immunoglobulins and responses to skin tests with DNCB, PPD, PHA and varicella antigen were within normal ranges in most of these children. Chemotherapy against leukemia was stopped for 2 weeks, from one week before to one week after vaccination. One child had a transient fever 10 days after measles vaccination, but no side reactions were observed in the others. Seroconversion was observed in all but one child who received measles vaccine, and neutralizing antibodies have persisted for at least 4 weeks and at most 3 years, when this study was terminated.

Effect of Timing of Measles Vaccination on Compliance with Immunizations During the Second Year of Life

J.L. Sherrod, R. Kane, J.D. Cherry, J. Fricker and K. Maples. J Pediatr 1983 Feb;102(2):186-90.

Authors' abstract: In 1976 the recommended time for routine measles immunization was changed from 12 to ≥15 months of age. Because of the known decrease in compliance with immunizations given during the second year of life and the scheduling of an additional visit close to the time of the diphtheria-tetanus-pertussis (DTP) booster immunization, the potential benefit from this change might be offset by a decrease in compliance in securing both measles vaccination and DTP booster immunization. A study of the change in immunization compliance was carried out in a county health facility and in a prepaid medical group practice. Charts of 795 infants (395 born before and 400 born after the change) were reviewed to assess the rates of compliance with measles and with DTP immunizations. Administration of measles vaccine at a scheduled time decreased by 10% ($0.05<p<0.06$) at the public health facility after the change in 1976 and by 13% at the prepaid group practice ($p<0.01$). This difference evened out in the public health facility patients by age 2 years, but a 9% decrease was still apparent at the prepaid medical group. A similar pattern was seen in compliance with the DTP booster immunization at each site. Any benefit derived by an increased measles seroconversion rate apparently was offset by an overall decrease in compliance for both measles and DTP booster immunizations.

Need for Measles Revaccination in Adolescents: Correlation with Birth Date Prior to 1972

A.S. Yeager, B. Harvey, F.J. Crosson, Jr., J.H. Davis, L.A. Ross and P.E. Halonen. J Pediatr 1983 Feb;102(2):191-5.

Authors' abstract: Measles hemagglutination inhibition (HI) antibody titers of less than 1:4 were significantly ($p<0.05$) more prevalent among subjects born from 1962 through 1971 and vaccinated with a single dose of live measles virus vaccine at 12 months of age (14.5%) than among subjects born during the same years but vaccinated at 13 months or older (2.3%). For subjects born in 1972 through 1976, however, this difference was not statistically significant; titers of less than 1:4 occurred in 6.2% of those vaccinated at 12 months, compared to 0% in those vaccinated at 13 months or older. A decline in maternally derived measles HI antibody may be related to the increased rate of HI antibody titers of 1:4 or greater following vaccination of more recently born subjects. Following revaccination of subjects whose measles HI antibody titers were less than 1:4, measles HI titers were lower than would be expected after successful primary vaccination. Nevertheless, measles HI antibody persisted at a level of 1:4 or more until the latest titer measurement of this study (one to two years after revaccination) in 87.5% of those whose initial vaccination had been at 11 or 12 months of age. No adverse reactions to revaccination occurred. Revaccination programs should be considered for adolescents and young adults born before 1972 who received live measles virus vaccine at or before 12 months. Children born from 1972 through 1976 who were vaccinated at 12 months or later are not in need of revaccination.

Data from Different Moscow Polyclinics on the Utilization of Vaccination Against Diphtheria, Pertussis, Tetanus, and Measles in Children of First 3 Years of Life (Russian)

N.L. Sukhorukova, M.P. Korzhenkova, L.A. Sigaeva, T.M. Zybina and N.M. Maksimova. Zh Mikrobiol Epidemiol Immunobiol 1982 Aug;(8):112-6.

English summary: The coverage of children by immunization against diphtheria, pertussis and tetanus during the first 3 years of life as indicated in forms No. 112 and No. 63 in 4 districts of Moscow was studied on the basis of the analysis of 1688 children's development histories. The coverage of children by immunization was found to be on the average 71.7%, fluctuating in individual districts from 58.6% to 85.9%. Immunization against measles covered 41.8% of children with fluctuations 24.2—51.2%. The most frequent reasons for the absence of prophylactic immunization in children during the first 3 years of life, or belated immunization in comparison with the specified terms, were contraindications due to neurological diseases (40.4%), exudative diathesis (15.9%) and recurrent viral infections (16.2%). Medical objections to immunization without sufficient grounds constituted 12.1% of all contraindications; among such objections those given by neuropathologists (9.8%) and pediatricians (2.3%) prevailed. To increase the coverage of children by immunization in the specified terms, the use of such measures as improving work with parents (explaining to them the importance of timely prophylactic immunization) and strict observance of instructions on medical contraindications may be considered most effective.

Frequency of Sister-Chromatid Exchanges in Children Vaccinated Against Measles

J. Castillo, G. Medina and A. Carnevale. Mutat Res 1983 Jan;119(1):65-9.

Authors' summary: The frequency of SCEs in lymphocyte culture of 10 children vaccinated against measles was studied. The mean frequency of SCEs/mitosis was 5.76 before and 5.32 after immunization. No significant difference was found between the 2 samples. As previously reported, we also found that the frequency of SCEs was lower than expected for F and G groups.

Measles Virus Panniculitis Subsequent to Vaccine Administration

B.E. Buck, L.C. Yang, M.H. Caleb, J.M. Greene, and M.A. South. J Pediatr 1982 Sep;101(3):366-73.

Authors' abstract: A severe illness developed gradually in a healthy boy following administration of live measles vaccine at age 14 years. Killed measles vaccine had been given at age 2. Panniculitis began near the site of live vaccine injection, extended contiguously to involve the entire upper arm, and then began to appear in distant subcutaneous sites. He was febrile, leukopenic, anemic, and lost weight rapidly. Evidence of a cause-and-effect relationship between the lesions and the measles vaccine included biopsy findings of particles closely resembling measles nucleocapsids and complete virions by electron microscopy, positive fluorescence after staining with two anti-measles nucleocapsid sera, and immunologic aberrations. The lesions regressed after various treatments and completely remitted on two occasions, but recurred. He became severely malnourished and finally died 29 months after the measles vaccination. At autopsy, panniculitis was found in the subcutis and mesentery, without evidence of involvement of the brain or other vital organs.

Allergic Reactions to Measles (Rubeola) Vaccine in Patients Hypersensitive to Egg Protein

J.J. Herman, R. Radin and R. Schneiderman. J Pediatr 1983 Feb;102(2):196-9.

Authors' abstract: We evaluated two children with allergy to egg-white protein (ovalbumin) who had generalized urticaria, angioedema, and respiratory difficulty after immunization with live rubeola vaccine. In both patients, serum IgE reactive with ovalbumin-related antigens in the vaccine was demonstrated. Subsequent evaluation of 24 children with ovalbumin allergy revealed that those who had positive ovalbumin skin tests, but no clinical reaction to egg white, were skin test negative on prick and intradermal testing with measles vaccine and were safely immunized. They had no detectable IgE directed against the rubeola vaccine, although IgE directed at ovalbumin was present. Six patients who had severe allergic hypersensitivity reactions on exposure to ovalbumin had IgE antimeasles vaccine antibody and had positive reactions after intracutaneous or intradermal testing with the vaccine. These patients were safely immunized with increasing volumes (0.05 ml increments every 20 minutes) of measles vaccine to receive the full dose. These studies suggest that children with severe allergic hypersensitivity to egg white should be screened with an intracutaneous test prior to immunization with measles vaccine; however, children who have positive skin tests but no clinical reaction to ovalbumin exposure are at minimal risk for hypersensitivity reactions to measles immunization, as previously reported.

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RUBELLA

General

An Outbreak of Congenital Rubella

L.G. Dales and J. Chin. West J Med 1981 Oct;135:266-70.

Authors' abstract: A large outbreak of rubella occurred in the San Francisco Bay Area in early 1979. Later that year and in early 1980, 13 cases of confirmed or probable congenital rubella syndrome were reported. Results of a subsequent investigation strongly suggest that these two events were related in a causal manner and do not represent an indirect association based on changes in diagnostic or reporting thoroughness. To prevent such episodes in the future, renewed emphasis must be placed on routine immunization of young children of both sexes, rigorous enforcement of school-entry immunization laws and selective immunization of women of childbearing age.

An Outbreak of Congenital Rubella in Chicago

C. Lamprecht, V. Schauf, D. Warren, K. Nelson, R. Northrop and M. Christiansen. JAMA 1982 Feb 26;247(8):1129-33.

Authors' abstract: After an outbreak of rubella in Chicago in 1978, an intensive survey of local health care personnel and hospital records identified 31 infants with congenital rubella syndrome (CRS). Rubella virus was isolated from 11 infants; rubella-IgM antibodies were demonstrated in seven infants; ten babies had persistent high rubella hemagglutination-inhibition (HI) titers. The incidence of CRS in Chicago between July 1978 and June 1979 was 48.9 per 100,000 live births. Mothers of babies with CRS frequently remembered a crash-illness during pregnancy (56%), were unmarried (74%), and were primigravidas (64%). No mother had received rubella vaccine. Review of prenatal rubella HI testing and follow-up immunization in one hospital showed that only eight (10.8%) of 74 seronegative women received rubella vaccine. Physicians need to place increased emphasis on detection and vaccination of susceptible adult women.

Clinical and Laboratory

Rubella Diagnostic Tests: What Is a Significant Result?

J.L. Sever and C. Cleghorn. Postgrad Med 1982 Mar;71(3):73-7.

From authors' introduction: Tests for rubella antibody are now widely used throughout the United States: Over 7.5 million are performed each year. A total of 22 different commercial kits for these tests have become available in the last few years and are being used by laboratories. The kits have introduced several new ways for reporting "titers" and seroconversions. In this article we review the appropriate use of the serologic tests for rubella and consider the six test methods generally available in the 22 kits. Table 1 lists relevant data for each of the kits, including the values signifying immunity and recent infection (seroconversion).

Staphylococcal Protein A in the Serologic Diagnosis of Congenital Rubella and Toxoplasmosis

T. Chonmaitree, K.R. Powell and M.A. Menegus. Pediatr Infect Dis 1982 Jul-Aug;1(4):228-31.

Authors' abstract: Staphylococcal protein A (SPA) has been used to remove maternal IgG from cord or neonatal sera to make serologic testing for congenital infection more IgM specific. To evaluate the clinical usefulness of this procedure, sera sent for TORCH titers that had rubella hemagglutination inhibition (RHI) reciprocal titers ≥8 or toxoplasmosis indirect fluorescent antibody (TFA) titers ≥16 were adsorbed with SPA and retested. Nine of 109 sera were TFA positive by routine testing, and all but one from an infant with congenital toxoplasmosis became negative after SPA adsorption. A repeat TFA at 4 to 26 months of age was negative in all six children without evidence of toxoplasmosis who returned for follow-up. Fifty of 55 sera were RHI positive by routine testing, and all but one from an infant with congenital rubella became negative after SPA adsorption. The repeat routine RHI was negative in 32 of 35 children whose sera were initially negative after SPA adsorption. SPA adsorption greatly increased the specificity of routine RHI and TFA tests in the diagnosis of congenital rubella and toxoplasmosis.

Consequences of Confirmed Maternal Rubella at Successive Stages of Pregnancy

E. Miller, J.E. Cradock-Watson and T.M. Pollock. Lancet 1982 Oct 9;2(8302):781-4.

Authors' abstract: Over a thousand women with confirmed rubella infection at different stages of pregnancy were followed up prospectively. Two-thirds of the women were multiparous. Pregnancy continued in 40%, and the infants were followed up after birth both clinically and serologically. The frequency of congenital infection after maternal rubella with a rash was more than 80% during the first 12 weeks of pregnancy, 54% at 13-14 weeks, and 25% at the end of the second trimester. The infection rate then rose again to reach a high figure in the last month. Follow-up was to 2 years of age—the findings in infected children being compared with those in children who had escaped infection. Rubella defects occurred in all infants infected before the 11th week (principally congenital heart disease and deafness) and in 35% of those infected at 13-16 weeks (deafness alone). No defects attributable to rubella were found in 63 children infected after 16 weeks. Continued surveillance of cases of confirmed rubella during pregnancy is recommended as an additional way of monitoring the effect of rubella vaccination.

Neurological Complications Following Rubella Infection

M. Bechar, S. Davidovich, G. Goldhammer, I. Machtey and N. Gadoth. J Neurol 1982;226(4):283-7.

Authors' abstract: Neurological complications following rubella are only rarely encountered. However, in many cases severe neurological impairment may occur, leading to permanent disability. In a recent epidemic of rubella in Israel during the years 1978-1979, 20 patients with severe neurological complications have been seen. We report on 5 cases of which 3 are described in detail. Considering the efficacy of immunization against rubella, we suggest that in countries such as England and Israel in which periodic epidemics of rubella occur, a generalized plan of immunization should be undertaken during the first years of life. Such an approach will prevent the neurological complication of congenital, as well as acquired, rubella infection.

Serologic Studies on the Association of Rubella Virus Infection and Juvenile Rheumatoid Arthritis

W. Al-Nakib and H.A. Majeed. Ann Trop Paediatr 1981 Jun;1(2):93-6.

Authors' abstract: Rubella hemagglutination-inhibition (HAI) and virus-specific IgM antibody responses were investigated in 26 patients with Juvenile Rheumatoid Arthritis (JRA) and 52 age- and sex-matched controls. 30.8% of patients with JRA showed no serological evidence of a previous infection by rubella virus (RV). In addition, the Geometric Mean Titers (GMT) of rubella HAI antibody among patients with JRA were similar to those found among the control group. Furthermore, rubella-specific IgM responses could not be detected in any of the sera among JRA patients or control children, although they were present in the sera of all 12 (100%) patients with clinical rubella. These data, therefore, fail to suggest serological evidence for the association of RV infection with JRA.

Chronic Arthritis Associated with the Presence of Intrasynovial Rubella Virus

R. Grahame, R. Armstrong, N. Simmons, J.M. Wilton, M. Dyson, R. Laurent, R. Millis and C.A. Mims. Ann Rheum Dis 1983 Feb;42(1):2-13.

Authors' abstract: In this report we present 21 instances in which live rubella virus was isolated from synovial fluid obtained from 6 cases of inflammatory oligoarthritis or polyarthritis over a period of 2 years in the absence of firm clinical evidence of rubella. In 3 cases (cases 1, 2, 6,) a persistent oligoarthritis predominantly affecting the knee joints occurred in 2 adult women and one man, lasting to date 27, 29, and 18 months, respectively, and in one of these cases virions were found in cells of the synovial membrane. In case 3 a boy of 9 presented with an illness indistinguishable from the systemic variety of juvenile chronic arthritis (Still's disease). In case 4 a young man with persistent monoarthritis was found to have ankylosing spondylitis, and in case 5 a progressive erosive polyarthritis developed 5 years after an attack of rubella complicated by rubella arthritis. The virus was identified by a variety of virological techniques and infection confirmed by immunofluorescence and (in one case) electron microscopy.

Radial Hemolysis for the Detection of Rubella Antibody in Acute Postnatal Rubella

P. Morgan-Capner, C. Burgess and S. Fisher-Hoch. J Hyg (Lond) 1982 Oct;89(2):311-20.

Authors' abstract: One hundred and forty-eight sera from 101 cases of acute postnatal rubella were examined by the radial hemolysis (RH) technique currently recommended by the Public Health Laboratory Service of the United Kingdom. In 75 cases the date of onset of rash was known. No sera were RH positive until the third day after the onset of rash and one serum was still negative at 9 days. By 10 days all sera gave a zone of at least 10 mm.

The antibody response detected by RH appears later than that detected by hemagglutination inhibition (HI). Thirty-nine of the 101 cases could be diagnosed by seroconversion or a significant rise in titer using the HI test (diagnosis of the remainder depending upon rubella-specific IgM tests). Using the RH test this figure rises to 48 but in ten of these cases reliance on RH would have meant a delay in diagnosis. The results also indicate that many more sera would need to be tested for rubella-specific IgM if the RH test was used instead of the HI test for evaluating possible cases and contacts of rubella.

Detection of Rubella Antibodies by Hemagglutination Inhibition, Indirect Fluorescent-Antibody Test, and Enzyme-Linked Immunosorbent Assay

M.V. Zartarian, G. Friedly, E.M. Peterson and L.M. de la Maza. J Clin Microbiol 1981 Dec;14(6):640-5.

Authors' abstract: Using hemagglutination inhibition (HAI) as a reference method, 292 (40 nonimmune, 252 immune) human serum samples were tested by indirect fluorescent antibody (IFA) and enzyme-linked immunosorbent assay (ELISA) for immune status and quantitation of rubella antibodies. The overall agreement with HAI for immune status was 99.7% (291/292) with IFA and 98.6% (288/292) with ELISA. Two specimens (0.7%, 2/292), negative by HAI, were equivocal by ELISA. Initially a 6.5% (19/292) overall disagreement was obtained for immune status evaluation between HAI and IFA, which was reduced to 0.3% (1/292) upon repeat testing. All of these samples were near the immune/nonimmune cutoff point (95 samples), reflecting an initial disagreement of 20% (19/95) in this category (HAI titers less than 1:20). Likewise, an initial overall disagreement of 4.5% (13/292) was obtained between HAI and ELISA which was reduced to 0.7% (2/292) upon repeated testing. Eleven of the 13 samples were near the immune/nonimmune cutoff point, reflecting an initial disagreement of 11.6% (11/95) with sera having an HAI antibody titer of less than 1:20. Quantitation of rubella antibodies by IFA showed an overall correlation with HAI of 86.6% within less than twofold titer and 99.3% within less than fourfold titers. In testing the ability of ELISA to quantitate antibody, a correlation coefficient (r) of 0.996 was obtained by plotting the measured average optical density (405 nm) of ELISA against the corresponding log of HAI titer. Both IFA and ELISA showed good correlation with HAI for immune status evaluation and for quantitation of rubella antibodies. Technically the HAI was the most cumbersome to perform, whereas IFA was the least technically demanding. Originally, 308 samples were tested; 16 samples (5.2%) could not be evaluated by IFA because of a high level of nonspecific fluorescence. The strict requirement of controlling the temperature range (23° to 24° C) during substrate hydrolysis proved to be a problem with the ELISA test in our laboratory.

Comparison of an Enzyme-Linked Immunosorbent Assay with Indirect Hemagglutination and Hemagglutination Inhibition for Determination of Rubella Virus Antibody: Evaluation of Immune Status with Commercial Reagents in a Clinical Laboratory

A.L. Truant, B.L. Barksdale, T.W. Huber and L.B. Elliott. J Clin Microbiol 1983 Jan;17(1):106-8.

Authors' abstract: Comparative evaluations of immune status for rubella virus are described for enzyme-linked immunosorbent assay, hemagglutination inhibition, and indirect hemagglutination. A 92.1% agreement between enzyme-linked immunosorbent assay and indirect hemagglutination assay was demonstrated for rubella immune status. Enzyme-linked immunosorbent assay and hemagglutination inhibition demonstrated a 92.6% agreement and were compared in an attempt to define the quantitative usefulness of comparisons of single sera for determining immune status. These data support the relative lack of correlation between single enzyme-linked immunosorbent assay and hemagglutination inhibition quantitative values. Enzyme immunoassay was, however, an acceptable alternative to hemagglutination inhibition for the determination of immune status to rubella virus.

Rapid Latex Agglutination Test for Rubella Antibody

J.L. Sever, N.R Tzan, I.C. Shekarchi and D.L. Madden. J Clin Microbiol 1983 Jan;17(1):52-4.

Authors' abstract: The latex agglutination card test (Rubascan) for the detection of rubella antibody was compared with the standard hemagglutination inhibition and enzyme-linked immunosorbent assay tests. There was complete agreement with sera which had hemagglutination inhibition titers of ≥16. Sera with low levels of antibody which were positive in the enzyme-linked immunosorbent assay, however, gave negative latex agglutination results approximately 25% of the time (false-negatives), whereas sera which were negative in the enzyme-linked immunosorbent assay gave false-positive results in about 3% of the cases. The use of capillary "finger stick" plasma instead of venous sera resulted in additional false-negative latex agglutination tests among patients with very low antibody titers. Because of the simplicity of the method, it should be possible to use this test in physicians' offices and in large immunization campaigns. Care should be taken to become completely familiar with the procedures and reading of the agglutination patterns. Control sera should always be used. Interpretation of results should take into consideration the rates of false-negative and false-positive results noted above. These rates apply to sera with little or no antibody. In particular, negative tests should be confirmed with more specific methods in critical cases, such as pregnant women exposed to rubella or women of childbearing age who are being considered for immunization. There was no problem with the latex agglutination findings for sera with higher titers. Since results are available in 8 minutes, physicians should be able to counsel their patients rapidly and immunize, if necessary, while the patient is still present.

Epidemiology

Rubella Outbreak in a Prenatal Clinic: Management and Prevention

P.E. Fliegel and W.M. Weinstein. Am J Infect Control 1982 Feb;10(1):29-33.

Authors' abstract: An obstetrician and two staff members developed rubella and exposed 56 susceptible pregnant women in a large prenatal and family planning clinic. Two women (3.6%) developed rubella at 27 and 38 weeks' gestation and delivered uneventfully. Sixteen hundred clinic and hospital employees were tested, with 79% of the total and 48 of 59 (81.4%) OB/GYN personnel showing prior infection and/or immunity (HAI titer ≥1:8). Of those susceptible, all obstetrical and most other personnel were vaccinated and removed from high risk areas until immune. Our management of a rubella outbreak and recommendations on hospital and clinic policy to avoid potential health problems are discussed.

Rubella Seroepidemiology in Hawaii

M.K. Serdula, M.R. Joesoef, A.C. Curtis, G. Kobayashi and N.H. Wiebenga. Int J Epidemiol 1982 Mar;11(1):31-8.

Authors' abstract: To determine rubella susceptibility levels 10 years after the introduction of the rubella vaccine in Hawaii, a large-scale serosurvey was conducted in conjunction with a campaign to raise the immunity levels of adolescent and adult women. Each woman tested for rubella antibody was asked her age, ethnic group, migration history, number of siblings, vaccination history, and the occupation of the head of the household. In the period from September 1977 through June 1979, serum specimens acceptable for analysis were collected from 3,852 women; 23.8% were susceptible (hemagglutination inhibition antibody titer less than 8) to rubella. A statistical analysis by fitting log-linear models revealed that rubella vaccination history, birthplace, ethnic group, number of siblings and island of residence appear to be factors related to rubella susceptibility. Although caution must be used in comparing this survey with previous surveys, the relatively low rubella susceptibility rate found in this survey may represent a true decrease in rubella susceptibility due to the rubella vaccination program.

Seroepidemiological Study on Rubella in Pregnant Women in Gondar Region, Northern Ethiopia

D. Sandow, G.S. Okubagzhi, U. Arnold and N. Denkmann. Ethiop Med J 1982 Oct;20(4):173-8.

Authors' abstract: Of 137 pregnant women (aged 15 to 36 years) from Gondar, northern Ethiopia, who were examined for rubella hemagglutination-inhibiting antibodies, 7.3% were seronegative. Seronegativity in the 15-17 year age-group was 16.7%; in the 18-30 year group 7%-9%; and in those over 30 years old, nil. From comparison of the findings with the results of other authors, it is concluded that the endemicity of rubella infections in Ethiopia resembles that in most other parts of the world.

Prevention and Control

Assessment of Susceptibility to Measles and Rubella

S.R. Preblud, F. Gross, N.A. Halsey, A.R. Hinman, K.L. Herrmann and J.P. Koplan. JAMA 1982 Feb 26;247(8):1134-7.

Authors' abstract: We conducted a serological and questionnaire study of 755 US Merchant Marine Academy cadets (aged 16 to 29 years) and their parents to determine the cadets' susceptibility rate to measles and rubella and to see if there was any difference in the accuracy of cadet and parental histories of previous infection and vaccination. Approximately 4% of the cadets were susceptible. We also determined the costs and the effectiveness of three alternative strategies for vaccinating susceptible adolescents and young adults: (1) vaccinating all persons regardless of past history; (2) serologically screening all persons and vaccinating only those who were susceptible; and (3) vaccinating all individuals who do not have physician-documented proof of proper vaccination, past infection (measles only), or serological immunity. The cost savings among the three alternatives are dependent on the proportion of potential vaccinees with records available for review and must be balanced against the proportion of susceptible persons protected by each alternative. We also found that a combined vaccination program for both measles and rubella is less costly than a program aimed at providing immunity to only one of the two diseases.

Rational Strategy for Rubella Vaccination

A.R. Hinman, K.J. Bart, W.A. Orenstein and S.R. Preblud. Lancet 1983 Jan 1;1(8314-5):39-40.

Authors' abstract: Current rubella vaccination programs, devised when knowledge of vaccine characteristics was still incomplete, have not been fully successful in protecting those at maximum risk of the sequelae of rubella infection. Now that more is known of vaccine characteristics and the impact of the initially chosen strategies has been assessed, it is time to modify immunization strategies, the priorities being first to protect women of childbearing age, and then to interrupt transmission of rubella.

Is Post-Partum Rubella Vaccination Worthwhile?

P.D. Griffiths and C. Baboonian. J Clin Pathol 1982 Dec;35(12):1340-4.

Authors' abstract: This study was designated to determine whether a program of screening for rubella antibodies during pregnancy, coupled with selective vaccination after delivery, could effectively increase herd immunity. One thousand women were studied when they returned for further antenatal care after having been screened, and possibly vaccinated, during an earlier pregnancy. Overall, the program was shown to be 83% effective since 108 women were truly seronegative in their initial pregnancies and 90 of them had been rendered immune by the time of their next pregnancy. The 18 failures of the program were attributed to the hemagglutination inhibition test employed (eight cases), failure to administer vaccine (seven cases) and true vaccine failures (three cases). Five pregnant women became infected with rubella virus during the study but all were in their initial pregnancies. All seronegative women were shown to follow the instruction not to become pregnant within three months of vaccination. We conclude that a program of screening for immunity, together with selective vaccination postpartum, can significantly reduce both the number of susceptible women and the number who experience rubella infection during pregnancy. Such programs should be vigorously encouraged as a means of helping to prevent congenital rubella.

Prevention of Rubella Transmission in Medical Facilities

W.L. Greaves, W.A. Orenstein, H.C. Stetler, S.R. Preblud, A.R. Hinman and K.J. Bart. JAMA 1982 Aug 20;248(7):861-4.

Authors' abstract: The widespread use of rubella vaccine in the United States has dramatically decreased the number of rubella cases and has prevented epidemics. Nevertheless, outbreaks of rubella continue to occur in medical facilities and have become important in the transmission of the disease. Control of outbreaks requires isolation of infectious patients, assignment of immune staff only to infectious patients, exclusion from work of infectious personnel, special follow-up of pregnant women and exposed persons, and the rapid vaccination of susceptible staff. Implementation of hospital rubella prevention programs is preferable to controlling an outbreak. The vaccination of all susceptible personnel provides the opportunity for preventing rubella outbreaks, disruption of hospital services, and fetal rubella infection.

Factors Influencing Participation in a Rubella Vaccination Program

D.L. Fischer, H.D. Jungkind and R.E. Nieman. Am J Infect Control 1982 Nov;10(4):121-7.

Authors' abstract: During the course of a 7-day voluntary rubella vaccination program conducted at a large community-teaching hospital, 718 hospital workers were vaccinated, an overall vaccination rate of 29%. During and after the vaccination campaign, physicians, employees, and students were surveyed as to their reasons for accepting or rejecting rubella vaccine. Prior to the campaign few hospital workers realized that rubella vaccination was of importance in their case. Although paycheck notices, newsletters, and poster displays were all effective in publicizing the campaign, hospital workers most frequently cited discussions with other workers as the major factor leading to their acceptance of vaccination. The belief that a history of rubella, diagnosed clinically, was adequate assurance of immunity was common among physicians and employees and was the major obstacle to greater success in the campaign. Vaccine reactions were infrequent and mild and did not lead to excessive employee absenteeism.

Effect of Rubella Vaccination Program in Schools on Rubella Immunity in a General Practice Population

D. Gilmore, E.T. Robinson, W.H. Gilmour and G.E. Urquhart. Br Med J [Clin Res] 1982 Feb 27;284(6316):628-30.

Authors' abstract: Between November 1979 and January 1980 all patients aged 13-21 years who attended a general practice in Glasgow were tested for their immunity against rubella (single radial hemolysis test). All of the women in the sample should have been vaccinated at 13 as part of the rubella vaccination program, which began in Glasgow in 1971. The program excludes boys. Of the 77 females and 64 male patients studied, nine (11.7%) and 10 (15.6%), respectively, were susceptible to the infection. For only 34 women was evidence of vaccination documented in the practice records, and three of those either had failed to seroconvert or had antibody below detectable values. Overall there were no significant differences between the proportion of men and women who were susceptible to the disease. The rubella vaccination program had clearly failed to reduce the number of susceptible women in this practice. Hence the immune state of all girls should be checked at about 15 years of age, so that as many as possible may be rendered immune before they leave school.

Rubella Immunity in Older Children, Teenagers, and Young Adults: A Comparison of Immunity in Those Previously Immunized With Those Unimmunized

R.G. Robinson, F.E. Dudenhoeffer, H.J. Holroyd, L.R. Baker, D.I. Bernstein and J.D. Cherry. J Pediatr 1982 Aug;101(2):188-91.

Authors' abstract: Because rubella continues to be a common illness in adolescents and young adults and because it has been suggested that booster rubella immunizations should be performed, we studied antibody prevalence in 459 predominantly adolescent patients in a pediatric group practice. Rubella antibody (PHA titer $\geq$1:13.5) in previously immunized patients (89.6% of 385) was significantly more common than antibody in unimmunized patients and patients with a questionable history of immunization (70.3% of 74) ($p<0.005$). Twenty-three seronegative patients with a documented history of prior immunization were reimmunized and 22 had an IgG (secondary) antibody response and only one an IgM (primary) antibody response. Since all but one of our patients with previous immunization had a secondary immune response following revaccination, it seems likely that the level of protection in previously vaccinated individuals is considerably greater than 90%. Attention today should be directed at finding and immunizing unvaccinated teenagers and young adults and not in major booster vaccine programs.

Rubella Screening and Immunization of Schoolgirls: Results Six to Seven Years After Vaccination

H. Zealley and E. Edmond. Br Med J [Clin Res] 1982 Feb 6;284(6313):382-4.

Authors' abstract: A long term follow-up study was carried out on girls given RA27/3 or Cendehill rubella vaccine in their 13th-14th year compared with a group of girls who had been found to be naturally immune at that age. A high proportion of the girls in all groups had persistent rubella antibody six to seven years after inclusion in the study, although some of these would have been considered to be susceptible to rubella by methods currently in use for screening for rubella antibody. Great care should be taken in interpreting the efficiency of the schoolgirl immunization policy in the United Kingdom; women in their childbearing years who may have received vaccine but are found by a screening test to be seronegative should be retested by a more sensitive procedure before a final report is made.

Rubella Vaccination: Persistence of Antibodies for Up to 16 Years

S. O'Shea, J.M. Best, J.E. Banatvala, W.C. Marshall and J.A. Dudgeon. Br Med J [Clin Res] 1982 Jul 24;285(6337):253-5.

Authors' abstract: Sera from 123 volunteers vaccinated six to 16 years previously with one of four rubella vaccines (Cendehill, RA27/3, HPV77-DE5, and To-336) were tested for rubella antibodies by single radial hemolysis and radioimmunoassay. By radioimmunoassay 110 (89.4%) of the vaccinees had antibody concentrations greater than the minimum immune titer (that is, $>15{,}000$ IU/l), 11 (8.9%) were seropositive but had concentrations $\leq15{,}000$ IU/l, and two (1.6%) were seronegative. Eight (6.5%) were seronegative by single radial hemolysis, of whom five had received Cendehill vaccine. Six to eight years after vaccination, subjects who had received Cendehill vaccine had the lowest geometric mean titer of antibody by radioimmunoassay while the subjects who had received HPV77-DE5 vaccine had the highest. Although antibody concentrations $\leq15{,}000$ IU/l were not detected among subjects given RA27/3 vaccine six to eight years previously, such low levels were detected in two (15.4%) vaccinated 11-16 years previously. These results emphasize the importance of long-term surveillance programs so that vaccination policies may be reviewed.

Rubella Immunization of Teenage Girls in Iceland and Follow-Up After a Severe Rubella Epidemic

B. Rafnar. Bull WHO 1982;60(1):141-6.

Author's abstract: Of 730 Icelandic schoolgirls, 12 years of age, screened for rubella antibodies by the hemagglutination-inhibition (H) technique, 372 (50.9%) were found to be seronegative. Rubella vaccine was administered to 355 members of this group, and to 12 girls with an HI titer of 20. Blood samples were taken 6 weeks and 1 year after immunization from 336 previously seronegative girls and from the 12 low-positive vaccinees, and tested for HI antibodies. The seroconversion rate was 99.15%. One year after immunization, 94.8% of the girls tested had an HI antibody titer of 40 or more. The geometric mean titer (GMT) of the previously seronegative girls was 62.07 at 6 weeks and 61.69 at one year after vaccination. Of the girls with an initially low positive titer, only 3 (25%) showed a significant rise. The GMT was 40 at 6 weeks, but fell to 25.2 after 1 year. Reimmunization had no effect on antibody levels in either group.

A severe rubella epidemic occurred 2 years after immunization, following which 345 vaccinees and 193 naturally immune controls were studied. All subjects had been exposed to wild rubella virus at school, and rubella cases had occurred in the homes of 116 vaccinees (33.6%) and 41 control subjects (21.2%). Only 5 (1.5%) primarily seronegative vaccinees and 2 unimmunized controls (1%) showed serological evidence of infection during the epidemic.

Effect of Immunization Against Rubella on Lactation Products. I. Development and Characterization of Specific Immunologic Reactivity in Breast Milk.

G.A. Losonsky, J.M. Fishaut, J. Strussenberg and P.L. Ogra. J Infect Dis 1982 May;145(5):654-60.

Authors' abstract: The development of an immune response to rubella virus in milk, serum, and nasopharyngeal secretions was studied in lactating postpartum women after immunization with HPV-77:DE5 or RA 27/3 live, attenuated rubella virus vaccine administered subcutaneously or intranasally. Over 69% of the women shed virus in milk after immunization. A predictable nasopharyngeal IgA and serum IgG antibody response to rubella virus was observed after subcutaneous or intranasal immunization with RA 27/3 vaccine. Little or no nasopharyngeal antibody response was seen after subcutaneous immunization with HPV-77:DE5 vaccine. A virus-specific IgA antibody response in milk was seen in all women. The presence of rubella virus in breast milk seemed to potentiate the peak levels of virus-specific antibody in the milk. Cellular immune reactivity to rubella virus in milk was observed in all vaccine groups. Thus, the virus-specific immune response induced in human milk after immunization with rubella virus vaccine may be intimately linked with the reactivity in bronchial lymphoid tissue.

Effect of Immunization Against Rubella on Lactation Products. II. Maternal-Neonatal Interactions

G.A. Losonsky, J.M. Fishaut, J. Strussenberg and P.L. Ogra. J Infect Dis 1982 May;145(5):661-6.

Authors' abstract: The transmission of rubella virus to newborn infants via the process of breast-feeding was studied after immunization of 16 breast-feeding and 10 non-breast-feeding mothers with HPV-77:DE5 live, attenuated rubella virus vaccine administered subcutaneously or RA 27/3 live, attenuated rubella virus vaccine administered intranasally or subcutaneously in the immediate postpartum period. Infectious rubella virus or virus antigen was observed in the breast milk of 11 (68%) of the 16 vaccinated, breast-feeding women studied. After maternal immunization, infectious rubella virus or virus antigen was recovered from the nasopharynx and throat of 56% of the breast-fed infants and from none of the non-breast-fed infants. Of the breast-fed infants, 25% showed transient seroconversion to rubella virus but without any clinical disease. No rubella virus-specific seroconversion was observed in the non-breast-fed infants. These observations provide strong support for the communicability of rubella virus to neonates via the process of breast-feeding.

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PREVENTION AND CONTROL

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INFLUENZA

General

Variability of the Virulent Properties of Influenza A Viruses in Recombination (Russian)

L.A. Zazimko, V.S. Vakin, I.A. Kozinets and N.G. Zakharova. Vopr Virusol 1982 Jul-Aug;27(4):449-52.

English summary: The pattern of redistribution of human virulence in epidemic strains of influenza viruses in recombination with human avirulent strains was studied. In the course of recombination of epidemic and attenuated influenza virus strains variants with different human virulence were obtained. Some recombinants manifested enforced reactogenic properties as compared with the epidemic strain (X/28, M/35, and 0/26—H1N1, and 2P—H3N2). At the same time, recombinants No 19 (H1N1) and 1P (H3N2) with a similar set of surface antigens were innocuous for man after intranasal administration. Using the observed differences in sensitivity to rimantadine as a marker of recombination, we obtained several sets of recombinants which had the antigenic structure of surface proteins of epidemic viruses and rimantadine sensitivity of the other parent.

Aerosol Treatment of Influenza

V. Knight. Cardiovasc Res Cent Bull 1981 Apr-Jun; 19(4):118-28.

Author's abstract: This report describes studies in mice and, preliminarily, in man of antiviral chemotherapy delivered deeply into the respiratory tract in small particle aerosol as a means of treatment for influenza that, if effective, could reduce illness and save many lives. Studies in mice showed remarkable therapeutic activity of ribavirin, amantadine, and of the two drugs given together in small particle aerosol in the treatment of influenza. Treatment of influenza A and B infection in man by this means was without significant toxicity, and recovery was prompt although the data were not sufficient to prove efficacy. The study will be continued in the 1980-1981 winter season.

Comparative Therapeutic Effect of Aerosolized and Oral Rimantadine HCl in Experimental Human Influenza A Virus Infection

F.G. Hayden, D.M. Zylidnikov, V.I. Iljenko and Y.V. Padolka. Antiviral Res 1982 Aug;2(3):147-53.

Authors' abstract: Thirty-six adult volunteers were inoculated intranasally with 7.2 $\log_{10}$ egg infectious doses 50% of an attenuated A/Khabarovsk/77/H1N1 virus. Twenty-four hours later volunteers were begun on both aerosol treatments (rimantadine HC1 25 mg in saline or saline, 10-minute exposure twice daily) and oral medications (rimantadine HC1 50 mg or placebo every 6 hours, three times daily) which were administered for 5 days. Virus-positive volunteers receiving placebo by both of the two routes had a peak in clinical illness scores on the second treatment day (mean score 5.3), which was not observed in either the aerosol rimantadine (0.6) or oral rimantadine (0.9) treated volunteers. On the second treatment day, the proportion of virus-positive volunteers with elevated axillary temperature measurements and the mean peak temperature measurement were also significantly reduced in both drug groups. No significant effects on the duration of virus shedding were noted. In experimental influenza A virus infection, characterized by mild clinical illness and short duration of virus shedding, low doses of aerosolized rimantadine had a therapeutic effect comparable to that found with larger doses of oral rimantadine.

Clinical and Laboratory

Viral Studies in Benign Acute Childhood Myositis

R.L. Ruff and D. Secrist. Arch Neurol 1982 May;39(5): 261-3.

Authors' abstract: Thirty-five cases of benign acute childhood myositis followed infections with influenza A or B. Two children had recurrent myositis associated with infections of different influenza types. None of the children had acute-phase antibody titers to the infecting type of influenza. These results are consistent with the proposal that benign acute childhood myositis can occur only with the initial infection of a viral type.

Mixed Infections with Influenza A and B Viruses

B. Tumova, V. Kasova and A. Stumpa. Acta Virol (Praha) 1981 Nov;25(6):418-9.

Authors' abstract: In the course of an influenza A and B epidemic, influenza virus was isolated from 46 patients. Seven of these patients showed seroconversion against influenza virus plus another respiratory virus. In 9 patients, simultaneous antibody increase against both influenza A and B viruses was demonstrated, but only a single virus type was isolated. In one case the isolated virus population could be separated into type A and B viruses.

Serological Diagnosis of Influenza B Virus Infection: Comparison of an Enzyme-Linked Immunosorbent Assay and the Hemagglutination Inhibition Test

R. Turner, J.L. Lathey, L.P. Van Voris and R.B. Belshe. J Clin Microbiol 1982 May;15(5):824-9.

Authors' abstract: The sensitivity of an enzyme-linked immunosorbent assay (ELISA) for the detection of antibody to influenza B virus was compared with that of the hemagglutination inhibition test on acute- and convalescence-phase sera obtained from adults and children infected with influenza B virus. Two whole virus, tissue culture-grown antigen preparations were used in the ELISA, influenza B/West Virginia/81 and influenza B/Hong Kong/72. Four antigens were used in the hemagglutination inhibition test. These included the tissue culture-grown whole virus antigens that were used in the ELISA. In addition the standard egg-grown antigens, influenza B/Singapore/79 and influenza B/Hong Kong/72, were included for comparison. The ELISA antibody titer was significantly correlated to the hemagglutination inhibition antibody titer, and 10 of 10 adults and 17 of 21 children infected with influenza B had fourfold antibody increases as detected by ELISA with either antigenic type of tissue culture-grown whole virus. Increases in geometric mean antibody titers of 16- to 71-fold were detected by ELISA. Increases in geometric mean antibody titers of 3- to 10-fold were detected by hemagglutination inhibition depending on the type of antigen utilized. We found that ELISA with whole virus antigens was a sensitive and specific test for the detection of antibody to influenza B virus.

Altered Theophylline Clearance During an Influenza B Outbreak

M.J. Kraemer, C.T. Furukawa, J.R. Koup, G.G. Shapiro, W.E. Pierson and C.W. Bierman. Pediatrics 1982 Apr;69(4):476-80.

Authors' abstract: During the 1980 influenza B outbreak in King County, Washington, 11 children whose asthma had previously been controlled with a stable theophylline dose, developed theophylline toxicity on this same dose. Two had seizures, eight had nausea and vomiting, and three had headaches. All had clinical evidence of a febrile viral illness. The toxicity appeared to be related to decreased theophylline clearance, which gradually returned to pre-illness levels over a period of one to three months. Six of ten children had serologic evidence of influenza B, which is presumed to be the cause of the altered clearance. In children receiving chronic theophylline therapy, symptoms of vomiting, headaches, or seizures during a viral illness may be due to theophylline toxicity rather than the virus. Such patients should have an immediate serum theophylline determination, even if previous levels have been in the therapeutic range.

Epidemiology

The Influenza Herald Wave

W.P. Glezen, R.B. Couch and H.R. Six. Am J Epidemiol 1982 Oct;116(4):589-98.

Authors' abstract: For three successive years (1976-1979), the community surveillance system of the Influenza Research Center identified a wave of influenza virus infections which occurred during the latter half of one epidemic period and which heralded the epidemic virus for the following year. Recognition of the herald waves required consistent and continuous sampling of respiratory illnesses occurring among persons who constituted a substantial proportion of the population of over two million people in Harris County, Texas. The herald wave infections consisted of only 0.4–2.0% of the 2500 to 3000 respiratory illnesses examined for virus. During the first two epidemic periods, the herald wave was easily detected as a wave of influenza B virus infections occurring during an influenza A virus epidemic and then a wave of influenza A virus infections during an influenza B virus epidemic. The third herald wave was obscured because it consisted of a small number of infections caused by viruses antigenically like A/Brazil/11/78 (H1N1) which occurred at the end of the outbreak caused by influenza A/USSR/90/77 (H1N1). The herald wave infections were detected among persons who lived in widely scattered areas of the county and who were representative of all age and socioeconomic groups. The herald wave phenomenon has the obvious benefit of providing information about the virus most likely to produce an epidemic during the next respiratory disease season. Under optimal conditions, this could allow six to nine months to prepare and administer control measures.

Association of Excess Mortality from Chronic Nonspecific Lung Disease with Epidemics of Influenza. Comparison of Experience in the United States and in England and Wales, 1968 to 1976

W.C. Blackwelder, D.W. Alling and C.H. Stuart-Harris. Am Rev Respir Dis 1982 May;125(5):511-6.

Authors' abstract: Mortality from chronic nonspecific lung disease reported in the United States and in England and Wales during the period 1968 to 1976 was studied to determine if excessive deaths from this condition were associated with epidemics of influenza. In both countries, peaks of excess mortality of this type did indeed occur during such epidemics; however, these excesses were considerably more marked in the British data where the estimated number of such deaths over the 8-year period was 15,800 compared with 6,000 for the United States. There was a decreasing secular trend in age-specific death rates for chronic nonspecific lung disease among British males of all ages, whereas only middle-aged males showed such a trend in the United States; older American males were subject to a substantially increasing trend. The respective trends in such mortality observed among males in the 2 countries were also seen among females but were smaller in magnitude.

Mortality and Influenza

W.P. Glezen, A.A. Payne, D.N. Snyder and T.D. Downs. J Infect Dis 1982 Sep;146(3):313-21.

Authors' abstract: Systematic virologic surveillance in Houston over the past seven years has revealed that influenza virus infections have been epidemic during each respiratory disease season. The peak of the occurrence of acute respiratory illnesses that caused patients to seek medical care always coincided with the peak of influenza virus activity. The peak number of deaths attributed to pneumonia or influenza followed the peak of influenza virus activity by about two weeks. This relationship was constant even though the time of the epidemic peak ranged from as early as the third week of December to as late as the second week of March. No increase in deaths occurred in the absence of influenza virus activity. Therefore, the methods used to predict base-line mortality that show a seasonal rise in the absence of influenza activity may be inaccurate and, if so, lead to underestimation of mortality associated with influenza virus infections.

Mortality During Influenza Epidemics in the United States, 1967-1978

K. Choi and S.B. Thacker. Am J Public Health 1982 Nov;72(11):1280-3.

Authors' abstract: Excess deaths due to pneumonia and influenza and excess deaths for all causes were estimated using a time-series analysis for each of the eight influenza epidemics in the United States that occurred between 1967-1978. The effects of different analytic methods and different methods of structuring data are compared. Future directions for estimating the impact of influenza on mortality include a combination of regression techniques and multiple time-series analyses of surveillance data.

Seroepidemiology of H1N1 Influenza: The Range of the Affected Population Is Widening

R. Pyhala and K. Aho. Med Biol 1982 Dec;60(6): 328-32.

Authors' abstract: The H1N1 influenza epidemic during the winter of 1980-81 affected a wider range of the population than the epidemics of 1977-78 and 1978-79. The increasing frequency of infection among elderly people can be explained by the antigenic drift in the surface proteins of the virus. Small children and pregnant women were affected to only a small extent by the first and second outbreaks, but they suffered more in 1980-81. This altered epidemiology may be explained by adaptation of the virus to the human host, but the genetic mechanism remains an open question.

Estimating Household and Community Transmission Parameters for Influenza

I.M. Longini, Jr., J.S. Koopman, A.S. Monto and J.P. Fox. Am J Epidemiol 1982 May;115(5):736-51.

Authors' abstract: A maximum likelihood procedure is given for estimating household and community transmission parameters from observed influenza infection data. The estimator for the household transmission probability is an improvement over the classical secondary attack rate calculations because it factors out community-acquired infections from true secondary infections. The mathematical model used does not require the specification of infection onset times and, therefore, can be used with serologic data which detect asymptomatic infections. Infection data were derived by serology and virus isolation from the Tecumseh Respiratory Illness Study and the Seattle Flu Study for the years 1975-1979. Included were seasons of influenza B and influenza A subtypes H1N1 and H3N2. The transmission characteristics of influenza B and influenza A (H3N2) and A (H1N1) outbreaks during this period are compared. Influenza A (H1N1), A (H3N2) and influenza B are found to be in descending order both in terms of ease of spread in the household and intensity of the epidemic in the community. Children are found to be the main introducers of influenza into households. The degree of estimation error from the misclassification of infected and susceptible individuals is illustrated with a stochastic simulation model. This model simulates the expected number of detected infections at different levels of sensitivity and specificity for the serologic tests used. Other sources of estimation error, such as deviation from the model assumption of uniform community exposure and the possible presence of superspreaders, are also discussed.

Cigarette Smoking as a Risk Factor for Epidemic A (H1N1) Influenza in Young Men

J.D. Kark, M. Lebiush and L. Rannon. N Engl J Med 1982 Oct 21;307(17):1042-6.

Authors' abstract: We studied an outbreak of A (H1N1) influenza in an Israeli military unit of 336 healthy young men to determine the relation of cigarette smoking to the incidence of clinically apparent influenza and to the influenza-antibody response. Of 168 smokers, 68.5 percent had influenza, as compared with 47.2 percent of nonsmokers ($p<0.0001$). Influenza was also more severe in the smokers; 50.6 percent of the smokers lost work days or required bed rest, or both, as compared with 30.1 percent of the nonsmokers. The proportion of all influenza in smokers that was attributable to smoking was 31.2 percent (95 percent confidence intervals, 16.5 to 43.1 percent). For severe influenza, the attributable risk in the smokers was 40.6 percent (95 percent confidence intervals, 21.6 to 54.8 percent). A quarter of all severe morbidity from influenza in the overall study population was attributable to smoking. Antibody levels to A/USSR/90/77 (H1N1) antigen were higher in smokers but not markedly so. We conclude that smoking is a major determinant of morbidity in epidemic influenza and may contribute substantially to incapacitation in outbreaks in populations that smoke heavily.

Impact of Type A Influenza on Children: A Retrospective Study

J.P. Mullooly and W.H. Barker. Am J Public Health 1982 Sep;72(9):1008-16.

Authors' abstract: Excess morbidity was studied during influenza A epidemics (1968-69, 1972-73) among children in a large prepaid group practice program. Excess rates of hospitalization for influenza-related conditions, primarily pneumonia and bronchitis, ranged from 5 per 10,000 (95 percent confidence limits (CL): 1 to 9) for non-high-risk children to 29 per 10,000 (95 percent CL: 5 to 53) for children with high-risk conditions. The relative increases in hospitalization rates were greatest for 5- to 14-year-old boys: 278 percent and 104 percent increases for high-risk and non-high-risk boys, respectively. The absolute increase was greatest for 0- to 4-year-olds. The excess rate of ambulatory medical care contacts, 2.6 per 100 (95 percent CL: −1.6 to 6.8 per 100) was not statistically significant. Excess hospitalization rates among 0- to 14-year-olds during epidemics were three to five times larger than those for persons between 15 and 64 years of age, but only one-fifth the rate of persons over age 65.

Nosocomial Influenza B Virus Infection in the Elderly

L.P. Van Voris, R.B. Belshe and J.L. Shaffer. Ann Intern Med 1982 Feb;96(2):153-8.

Authors' abstract: A hospital-acquired outbreak of influenza-like illness that involved 29 patients during 4 weeks was detected in March 1980. The average age of the patients was 63 years. Eighteen of the 29 patients with symptoms had influenza B virus infection documented by virus isolations, fourfold or greater hemagglutination inhibition antibody increases, or both. The attack rate among all hospitalized inpatients was 20%. Absenteeism of the hospital staff because of influenza-like illnesses preceded the outbreak by several weeks, suggesting staff-to-patient transmission. The patients' sera during acute illness had low hemagglutination inhibition antibody titers (geometric mean titer of 1:21) against contemporary influenza B virus antigens, indicating that the patients were highly susceptible to influenza B virus. Only one patient had received trivalent influenza vaccine during the preceding year. The excess hospital cost resulting from the outbreak was $13,270 or $458 per patient. Our observations show that the elderly are at risk of developing nosocomial influenza B virus infection and that these illnesses are costly. Continued efforts to develop efficient influenza immunization programs for elderly persons and hospital staff are worthwhile.

Impact of Influenza A in a Nursing Home

R.A. Goodman, W.A. Orenstein, T.F. Munro, S.C. Smith and R.K. Sikes. JAMA 1982 Mar 12;247(10):1451-3.

Authors' abstract: Outbreaks of influenza A in the institutionalized elderly have been reported only rarely. Such an outbreak occurred in a nursing home in the period December 12, 1980, through January 21, 1981. Thirty (25%) of the 120 residents had onset of influenza-like illness during the outbreak. Influenza A/Bangkok/79-like (H3N2) virus was isolated from throat swab specimens from five of eight acutely ill patients. Thirteen persons were hospitalized; nine persons died (case-fatality ratio, 30%). This outbreak documents that mortality associated with an influenza outbreak can be substantial in a closed population of the elderly. Because nursing home residents are an easily accessible high-risk population, control and prevention of influenza should be a high priority in nursing homes.

National Surveillance for Reye Syndrome: A Five-Year Review

E.S. Hurwitz, D.B. Nelson, C. Davis, D. Morens and L.B. Schonberger. Pediatrics 1982 Dec;70(6):895-900.

Authors' abstract: National surveillance for Reye syndrome conducted during five years, including the period 1973-1974 and December 1976 through November 1980, has resulted in the reporting of more than 2,000 cases of Reye syndrome. The highest reported incidence of Reye syndrome occurred during years of primary influenza B and A (H1N1) activity; the reported incidence during one period of influenza A (H3N2) activity was somewhat lower. Regional outbreaks of Reye syndrome have been associated with influenza A (H1N1) and B but now with influenza A (H3N2). Cases of Reye syndrome in whites tend to be distributed throughout all age groups whereas a large percentage of cases in blacks have been reported in infants less than 1 year of age in three of the past four years. Nationally, there has been a decline in the case-fatality ratio in recent years.

Prevention and Control

A Controlled Trial of Amantadine and Rimantadine in the Prophylaxis of Influenza A Infection

R. Dolin, R.C. Reichman, H.P. Madore, R. Maynard, P.N. Linton and J. Webber-Jones. N Engl J Med 1982 Sep 2;307(10):580-4.

Authors' abstract: Four hundred fifty volunteers participated in a placebo-controlled, double-blind, randomized trial of the prophylactic effects of rimantadine and amantadine during an outbreak of influenza A. The subjects received drugs orally at a dose of 100 mg twice a day for six weeks. Influenza-like illness occurred in 41 percent of the subjects receiving placebo but in only 14 percent of those receiving rimantadine and 9 percent of these receiving amantadine ($p<0.001$ for either drug vs. placebo). Laboratory-documented influenza occurred in 21 percent of placebo recipients, 3 percent of rimantadine recipients, and 2 percent of amantadine recipients ($p<0.001$). These findings represent efficacy rates of 85 percent for rimantadine and 91 percent for amantadine, as compared with placebo. More recipients of amantadine (13%) than recipients of rimantadine (6%; $p<0.05$) or placebo (4%; $p<0.01$) withdrew from the study because of central-nervous-system side effects. On the basis of this study, rimantadine appears to be the drug of choice for the prophylaxis of influenza A.

Potential for Single High-Dose Influenza Immunization in Unprimed Children

P.A. Gross, G.V. Quinnan, P.F. Gaerlan, C.R. Denning, A. Davis, M. Lazicki and M. Bernius. Pediatrics 1982 Dec;70(6):982-6.

Authors' abstract: High concentrations of split-product vaccine (SPV) are more immunogenic than lower concentrations. These studies were verified with another influenza strain, B/Singapore/22/79. Two ether-treated SPVs were compared in 80 children and young adults. The vaccine strains were influenza A/Bangkok/79, A/Brazil/78, and B/Singapore/79; 44 patients received a high-dose SPV containing 7, 7 and 60 micrograms each of the respective hemagglutinins (HA) and 36 received a standard dose SPV containing 7, 7, and 7 micrograms of HA, respectively. Among persons initially seronegative by hemagglutination inhibition (HAI) tests, the geometric mean titer (GMT) in 15 recipients of one high dose was 97 vs GMT of 37 in 18 recipients of one standard dose ($p<.05$). Furthermore, 87% of high-dose recipients had HAI titer $\geqslant 40$ vs 44% of standard dose recipients. In initially seropositive persons, GMT in 29 recipients of one high dose was 170 vs GMT of 84 in 18 recipients of one standard dose ($p<.05$). Immune response to the other two virus strains was comparable for the two vaccines. The reaction index for the high dose vaccine was 0.70 vs 0.45 for the standard dose (p=ns). An A/Bangkok epidemic struck the New York metropolitan area. The attack rate in unvaccinated matched sibling control subjects was 35% (15/43). There were no vaccine failures. In conclusion, in the small number of patients studied, a 60-micrograms HA dose of B/Singapore/79 was significantly more immunogenic than a standard 7-micrograms HA dose without an increase in reactogenicity.

Clinical Reactions and Serologic Responses after Vaccination with Whole-Virus or Split-Virus Influenza Vaccines in Children Aged 6 to 36 Months

D.I. Bernstein, J.M. Zahradnik, C.J. DeAngelis and J.D. Cherry. Pediatrics 1982 Apr;69(4):404-8.

Authors' abstract: The reactogenicity and immunogenicity of whole-virus and split-product influenza vaccines were studied in 77 children between the ages of 6 and 36 months. Subjects initially received monovalent vaccine containing either A/USSR/77 (H1N1) antigen in 1978 or A/Brazil/78 (H1N1) antigen in 1979. One month later a trivalent preparation was given which contained the respective H1N1 antigen plus A/Texas/77 (H3N2) and B/Hong Kong/72 antigens. Temperatures $\geqslant 37.8$ C ($\geqslant 100$ F) were observed more commonly after initial vaccination with whole-virus vaccine (35%) than after split-product vaccine (14%). No child had a temperature of $\geqslant 39.4$ C (103 F) or a febrile convulsion. The trivalent vaccines were more reactogenic than the monovalent vaccines although none of the reaction indices exceeded 0.9. The whole-virus vaccine appeared to be more immunogenic, especially in those children who were initially seronegative (preimmunization hemagglutination-inhibiting antibody titer <5). Only 50% of children vaccinated with split-product vaccines with initial hemagglutination-inhibiting titers <5 achieved titers $\geqslant 20$ to the H1N1 antigen after two doses of vaccine compared with 97% in similar whole-virus vaccine recipients. The degree of antibody response to the A/Texas/77 component of the vaccines was greater than the response to the A/Brazil/78 or A/USSR/77 antigens.

Cold-Adapted Recombinant Influenza A Virus Vaccines in Seronegative Young Children

P.F. Wright, N. Okabe, K.T. McKee, Jr., H.F. Maassab and D.T. Karzon. J Infect Dis 1982 Jul;146(1):71-9.

Authors' abstract: Two live, attenuated, intranasally administered influenza virus vaccines were evaluated in 21 seronegative young children at Vanderbilt Children's Hospital (Nashville, Tennessee). The vaccines were derivatives of a cold-adapted master strain, influenza A/Ann Arbor/6/60 virus, containing the hemagglutinin and neuraminidase of one of two contemporary strains, influenza A/Hong Kong/123/77 (H1N1) or A/Alaska/6/77 (H3N2) virus. Both vaccine strains replicated in seronegative young children without evidence of genetic instability. In addition, both vaccine strains caused no identifiable clinical reactions, were not transmitted to other seronegative children, and gave long-lasting immunity. In a subsequent naturally occurring epidemic of influenza A/Bangkok (H3N2) virus, children previously vaccinated with the related strain, influenza A/Alaska (H3N2) virus, were significantly protected as judged by serologic evidence of reinfection.

Persistence of Antibody after the Administration of Influenza Vaccine to Children with Cancer

C.V. Sumaya and T.E. Williams. Pediatrics 1982 Feb; 69(2):226-9.

Authors' abstract: Children with cancer who received an intramuscular injection of inactivated split or whole bivalent (A/New Jersey/76-A/Victoria/75) influenza virus vaccine during the fall of 1976 were tested up to 18 months later for the persistence of antibody. Titers of antibody $\geqslant 10$ to influenza A/New Jersey/76 virus were present in the sera of 34 children two weeks after immunization. The geometric mean titer was 40.0. Eighteen months later a titer $\geqslant 10$ was present in 13 (38%) children; the geometric mean titer was 8.5. Of 36 children with a titer of antibody $\geqslant 10$ to A/Victoria/75 virus two weeks after immunization, 34 still had a detectable titer in the later examination. The geometric mean titer declined from 65.3 to 25.6. Titers of antibody to B/Hong Kong/72 virus (not included in the vaccine) remained relatively stable. In 11 children the usual chemotherapy was discontinued during the study. The shorter persistence of antibody to A/New Jersey/76 virus, in contrast to that of the other two influenza viruses tested, was associated with a lack of prior exposure to the virus and the absence of subsequent natural infection with this virus or an antigenically related subtype. The potential effect of cancer chemotherapy on the persistence of antibody levels is unclear.

Influenza Vaccination in Patients with Chronic Renal Failure

J. Nikoskelainen, P. Vaananen, J. Forsstrom and A. Kasanen. Scand J Infect Dis 1982;14(4):245-51.

Authors' abstract: 27 patients with chronic renal failure (CRF), 12 of whom were on maintenance hemodialysis, and 40 healthy control individuals were immunized with a split-type influenza vaccine containing A/Victoria/75 (H3N2), A/USSR/77 (H1N1), B/Hong Kong/73 antigens; 2 doses were given 4 weeks apart. Antibody responses were determined by the single radial hemolysis (SRH) technique. After immunization a significant rise (increase in SRH $\geqslant 2$ mm) was measured to A/Victoria in 11 (73%) azotemic and in 11 (92%) hemodialyzed patients and in 35 (88%) controls. To B/Hong Kong a significant antibody rise was observed in 10 (67%) azotemic, in 11 (92%) hemodialyzed and in 27 (68%) control individuals. The mean prevaccination and postvaccination antibody titers in patients with CRF, either azotemic or hemodialyzed, were significantly lower than in healthy control individuals to both A/Victoria and B/Hong Kong antigens ($p<0.001$). On the other hand the mean antibody rises after vaccination were of the same magnitude in all groups. The patients on maintenance hemodialysis had lower prevaccination antibody titers but the postvaccination mean titers were slightly higher than in the azotemic patients. No adverse reactions to the vaccination or deterioration of the renal function were observed; thus we recommend an annual vaccination of patients with CRF.

Prevention of Influenza in the Elderly

F.L. Ruben. J Am Geriatr Soc 1982 Sep;30(9):577-80.

Author's abstract: A gradual evolution has occurred in the development of influenza vaccines to their present highly purified state. Although studies are limited and vaccines are far from perfect, influenza vaccines should be used in the geriatric age group. Chemoprophylaxis is currently available against influenza A; however, studies should be made of its safety and efficacy in the elderly. Because of the severe consequences of influenza in aged persons, there is need for continued evaluation of vaccines, improved delivery, improved education, and new strategies for the prevention of influenza in the elderly.

Influence of Trivalent Influenza Vaccine on Serum Theophylline Levels

R.G. Fischer, B.H. Booth, D.Q. Mitchell and A.H. Kibbe. Can Med Assoc J 1982 Jun 1;126(11):1312-3.

Authors' abstract: Recently Renton and associates reported significant increases in serum theophylline levels in patients who had received trivalent influenza vaccine: however, they studied only seven patients (three with chronic obstructive lung disease and four healthy volunteers) and did not conduct a long-term follow-up. We therefore selected 12 patients with asthma who were taking long-acting theophylline and studied their serum theophylline levels for 2 weeks after they had received the vaccine.

The study results suggest that physicians may use trivalent influenza vaccine for patients receiving long-acting theophylline, but that they should observe the patients closely after vaccination.

Guillain-Barré Syndrome in the United States, 1979-1980 and 1980-1981. Lack of an Association with Influenza Vaccination

J.E. Kaplan, P. Katona, E.S. Hurwitz and L.B. Schonberger. JAMA 1982 Aug 13;248(6):698-700.

Authors' abstract: An ongoing surveillance program was intensified during the 1979-1980 and the 1980-1981 influenza seasons to determine whether an increased risk of acquiring Guillain-Barré syndrome (GBS) within eight weeks after influenza vaccination existed for adults in the United States who received influenza vaccine, when compared with adults who had not been vaccinated recently. Five hundred twenty-eight cases of GBS with onset between September 1 and March 31, including seven following recent vaccination, were reported by participating neurologists in 1979-1980; 459 cases, including 12 following recent vaccination, were reported in 1980-1981. The relative risk of acquiring GBS following influenza vaccination—0.6 in 1979-1980 and 1.4 in 1980-1981—was not significantly different from 1.0 in either season. These results suggest that there was no increased risk of acquiring GBS associated with the influenza vaccines administered during these seasons and that the causative "trigger agent" in the A/New Jersey (swine) influenza vaccine administered in 1976 has not been present in subsequent influenza vaccine preparations.

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DIPHTHERIA—PERTUSSIS—TETANUS

General

Studies on the Stability of Tetanus and Pertussis Components of DPT Vaccine on Exposure to Different Temperatures

V. Kumar, G. Sahai, P. Gupta and A. Kumar. Indian J Pathol Microbiol 1982 Jan;25(1):50-4.

Authors' abstract: Potency is an essential prerequisite for any immunobiological, so that no deterioration may occur with reasonable time when the product is exposed to ambient temperature in the field. The effect of various storage conditions on pertussis and tetanus components of diphtheria, pertussis and tetanus vaccine (DPT vaccine) was examined. Potency of these components was determined with a view that vaccine may get affected adversely during exposure to ambient temperature in transit and also due to inadequate cold chain and storage facilities at the peripheral health centers. The present study showed that there is no significant deterioration of potency of tetanus component when vaccine was kept at 22° C for 45 days. However, at 35° C the product did show slight deterioration although the potency still remained within acceptable limits. The potency of pertussis component was not adversely affected up to 45 days even at 35° C in the present work. The fluctuations in potency results for both components were not statistically significant. At 45° C temperature, both tetanus and pertussis components in DPT vaccine showed significant deterioration of potency at various time intervals.

Humoral Immune Response in Vitamin A Deficient Children

P.M. Kutty, M. Mohanram and R. Vinodini. Acta Vitaminol Enzymol 1981;3(4):231-5.

Authors' abstract: Humoral immune response was evaluated in children with vitamin A deficiency. The percentage of B lymphocytes and the initial levels of plasma IgA, IgG and IgM were normal. Two weeks after immunization with diphtheria and tetanus toxoids, there was a marked increase in the antibody titers. There were no significant differences between the deficient and the normal children. The results indicate that the antibody production is not altered in children with vitamin A deficiency.

Diphtheria-Tetanus Toxoid-Pertussis Vaccination and Sudden Infant Death in Tennessee

R.H. Bernier, J.A. Frank, Jr., T.J. Dondero, Jr. and P. Turner. J Pediatr 1982 Sep;101(3):419-21

Authors' abstract: A temporal association between DTP vaccination with a specific DTP test and SIDS was noted in Tennessee. Eleven infants died within 8 days of vaccination in the study period compared to three infant deaths within 8 days of vaccination during the control period when the suspect lot was not in use. Nine of the 11 infants dying within 8 days during the study period had received the suspect lot; of these, four had died within 24 hours of vaccination. The differences in the number of vaccinated infants dying within 8 days or within 24 hours of vaccination with the suspect lot during the study period and with any lot during the control period were not statistically significant at the .05 level (p=.063 and .066, respectively). Restricting the analysis to the study period and using the binomial distribution, the probability of having observed four or more deaths on any single one of the first 8 days after use of lot A is .03.

Evidence is sufficient to indicate that an unusual clustering of SIDS cases occurred shortly after vaccination with the suspect lot. This was due either to chance, or to the vaccine used. The suspect vaccine lot was found to be acceptable with regard to potency and freedom from toxicity for all components. No other evidence was uncovered to support a causal relationship between the suspect lot and SIDS.

Muscle Granulomas Following Intramuscular Injection

R.E. Mrak. Muscle Nerve 1982 Oct;5(8):637-9.

Author's abstract: An 8-month-old child underwent a muscle biopsy because of hypotonia. The biopsy showed centronuclear myopathy and, in addition, an unusual granulomatous inflammatory infiltrate. The child died of respiratory complications and a complete autopsy failed to reveal further evidence of granulomatous disease. The lesion was reproduced in experimental animals by intramuscular injection of diphtheria and tetanus toxoids and pertussis vaccine. Granular material present in histiocytes in these lesions was shown histochemically to be an aluminum salt.

Streptococcal Abscesses Following Diphtheria-Tetanus Toxoid-Pertussis Vaccination

W.L. Greaves, A.R. Hinman, R.R. Facklam, K.C. Allman, C.L. Barrett and H.C. Stetler. Pediatr Infect Dis 1982 Nov-Dec;1(6):388-90.

Authors' abstract: Abscesses developed in seven children who received diphtheria-tetanus toxoid-pertussis vaccine at a clinic in Indiana. Epidemiologic investigation revealed that all seven children had received vaccine from the same multidose vial and had been vaccinated by the same nurse at the office of one physician. Group A beta-hemolytic Streptococcus was isolated from abscesses in six of the seven children. No source was identified as the cause of this cluster of abscesses. Vaccine of the same lot number used elsewhere was not associated with the development of abscesses. It appears that the vaccine became contaminated during use.

Incidence and Type of Reactions to Triple Antigen (DTP) and DT (CDT) Vaccines

B.J. Feery. Med J Aust 1982 Nov 27;2(11):511-5.

Author's abstract: Local and general reactions were significantly more common in infants given DTP (triple antigen) vaccine than in those given DT (diphtheria and tetanus) vaccine. In 7712 DTP immunizations and 335 DT immunizations studied prospectively, local reaction rates were 47.8% and 33.7%, and general reaction rates were 38.4% and 10.1% respectively. The most commonly reported general reactions after both vaccines were irritability and fever. Persistent screaming was reported in 7.4% and 1.5% of vaccinees, and pallor or hyporesponsiveness in 1% and 0.3% respectively. Two infants developed convulsions and one suffered attacks of twitching after DTP immunization. No persisting sequelae were detected.

Diphtheria

Tetracycline Resistance of *Corynebacterium diphtheriae* Isolated from Diphtheria Patients in Jakarta, Indonesia

R.C. Rockhill, Sumarmo, H. Hadiputranto, S.P. Siregar and B. Muslihun. Antimicrob Agents Chemother 1982 May;21(5):842-3.

Authors' abstract: Of 133 *Corynebacterium diphtheriae* isolates from diphtheria patients in Jakarta, Indonesia, 86% were resistant to ≥32 μg of tetracycline per ml. All isolates were sensitive to ampicillin, cephalothin, chloramphenicol, clindamycin, penicillin, erythromycin, and kanamycin. The general resistance of *C. diphtheriae* to tetracycline in this part of Indonesia appears to be unique compared with resistance reported in studies done in other parts of the world.

Bacterial Endocarditis Due to *Corynebacterium diphtheriae* (French)

C. Senaneuch, E. Reverdy, A. Bozio, P. Monnet, M. Chuzel and H. Termet. Arch Fr Pediatr 1982 Mar;39(3):165-8.

English summary: A case of bacterial endocarditis with unusual features in a 5-year-old boy is reported. There was no underlying heart disease or provocating factor. The organism was a non-toxigenic *Corynebacterium diphtheriae* which was difficult to classify. It appeared to be close to the JK group of Corynebacterium described by the Center for Disease Control and considered as possibly responsible for severe infections. However, it was sensitive to penicillin. The course of the disease was complicated by the destruction of coronary valves and by splenic infarctus. Replacement of the aortic valve with a prosthesis was necessary. The boy was finally cured but the outcome remains uncertain.

Level of Immunity Against Diphtheria Among the Personnel of a Hamburg Hospital and in the Normal Population (German)

H. Allerdist. Dtsch Med Wochenschr 1981 Dec 25;106(51-52):1737-41.

English summary: Diphtheria antitoxin titers were measured by passive hemagglutination in a total of 4542 blood samples obtained between the end of 1980 and beginning of 1981 from staff at Hamburg hospitals and from randomly selected age-matched persons (1219). Among the hospital personnel, 67.5% had no protective diphtheria antitoxin (≤0.11 IU/ml), compared with 52% among the control group. Among those aged 15-24 years, 60.2% of staff were unprotected, compared with 46.6% of the control population. The geometric mean value of the diphtheria antitoxins also gave a worse immunity level for hospital personnel (0.08 IU/ml) than the control population (0.14 IU/ml). While geometric mean titer values of hospital staff beyond the age of 45 fell nearly continuously, those in the control population rose with increasing age.

Immunity Against Diphtheria in Mothers and Their Newborns in Hamburg (1980) (German)

W. Ehrengut and J. Tegeler. Monatsschr Kinderheilkd 1982 Oct;130(10):775-7.

English summary: The diphtheria antitoxin level (indirect hemagglutination) was measured in blood samples of 185 mothers and their newborns. Protective titers ($\geq$0.1 I.U. diphtheria antitoxin/ml) were found in 29.2% of the confined women and in 27% of their newborn babies. A review of similar investigations from the literature is given, and diphtheria toxoid boosters are recommended for youngsters and adults to improve the relatively poor immunity status against diphtheria in the population.

Diphtheria Immunity in Mali: Mothers and Their Neonates and Children Under Two Years of Age

H. Allerdist, W. Ehrengut and Y. Fofana. Tropenmed Parasitol 1981 Dec;32(4):274-5.

Authors' abstract: An analysis of diphtheria antibodies (indirect hemagglutination technique) in 85 paired sera of Malian mothers and their newborns (cord blood) showed that all mothers had protective antibody levels (>0.1 I.U./ml). Eighty-one percent of the neonates demonstrated protective immunity towards diphtheria. Since in Mali respiratory diphtheria is rare, it may be assumed that a silent immunization by skin sores contaminated with diphtheria germs takes place. This assumption is supported by an analysis of 30 unimmunized 6- to 24-month-old babies, 10 of whom had protective and 16 low levels of diphtheria antibodies in their sera. By inclusion of 13 further children of the same age group (possibly previously immunized, since they had demonstrable antibodies against tetanus) we found a geometric mean diphtheria antibody titer for all 43 children of 0.08 I.U./ml.

A Comparative Clinical Study of Adsorbed Tetanus Vaccine and Adult-Type Tetanus-Diphtheria Vaccine

S.P. Deacon, D.T. Langford, W.M. Shepherd and P.A. Knight. J Hyg (Lond) 1982 Dec;89(3):513-9.

Authors' abstract: A limited assessment of immunity to diphtheria revealed that only 44.8% of adults had protective levels (>0.01 U/ml) of diphtheria antitoxin in their sera. In the light of this information, it was decided to assess the suitability of Adult-type Tetanus-Diphtheria Vaccine as a replacement for Adsorbed Tetanus Vaccine in occupational health schemes. A comparative study of these vaccines showed that a single dose of each produced an equivalent rate and level of tetanus antitoxin responses. Adult-type Td Vaccine elicited more than fourfold increases of diphtheria antitoxin in 76% of vaccinees. No statistically significant differences were observed in the clinical reactivity of the vaccines under test. However, the combined vaccine caused a slightly higher incidence of local reactions (pain, redness and swelling) while recipients of Adsorbed Tetanus Vaccine more frequently experienced pain.

Immunization of Adults During an Outbreak of Diphtheria

S.R. Palmer, A.H. Balfour and A.E. Jephcott. Br Med J [Clin Res] 1983 Feb 19;286(6365):624-6.

Authors' abstract: In an outbreak of infection due to *Corynebacterium diphtheriae* in a hospital for mentally subnormal adults, sera from 211 members of staff were screened for diphtheria antitoxin titers. Of these, 79 (37%) required immunization, and a low dose preparation (1 LfU of diphtheria and 10 LfU tetanus toxoids) was offered. Of the 64 subjects who accepted a single immunization and were subsequently retested, seroconversion to diphtheria toxoid occurred in 45 (70%), the rate being highest in younger adults. Seroconversion to tetanus toxoid occurred in 59% of subjects. Local reactions to the single dose were reported by 29 (43%) subjects, and nine (13%) experienced moderately severe local reactions and systemic symptoms. We conclude that adults should not be vaccinated without previous screening for susceptibility to diphtheria; that neither previous immunization nor age is reliable in predicting the need for vaccination; and that though a single booster dose of diphtheria toxoid is probably effective in adults under 45, two doses should be given to those in the older age group.

Seroconversion in Juvenile Patients and Adults after Diphtheria Immunization (German)

H. Allerdist and J. Ehrengut-Lange. Dtsch Med Wochenschr 1982 Nov 19;107(46):1755-60.

English summary: A total of 155 Hamburg hospital personnel aged between 15 and 64 years were immunized against diphtheria. Out of 120 prevaccination seronegative persons (including very low diphtheria antitoxin titers), 92 (76.7%) reacted with seroconversion above the diphtheria protection level after the adult dosage of 7.5 IU diphtheria toxoid. Good results were still obtained with a 2.5 IU dosage. The conversion factor of 210 in the age group of 55- to 64-year-old persons was sevenfold higher than in the 15- to 24-year-old group. Local reactions of a mainly slight nature were seen after vaccination in 20.8%, only one immunized person showed a slight increase of temperature. It is recommended to offer reimmunization with a 7.5 IU dosage to students before they leave school. Selective immunization of certain professional groups, such as hospital personnel, should be performed according to age and history, either with 7.5 or 2.5 IU of diphtheria toxoid.

Prophylactic Inoculations and Seizure Activity in the EEG (Polish)

S. Cizewska, Z. Huber and W. Suzewski. Neurol Neurochir Pol 1981 Sep-Dec;15(5-6):553-7.

English summary: Bioelectric activity of the brain was investigated after diphtheria-tetanus vaccination in healthy children. Seventeen healthy, randomly selected children aged 6-7 and 14 years were studied. EEG investigations showed appearance of significant changes in 13 out of 17 children. The main finding was appearance of previously absent or intensification of previously present seizure activity. Serial recording obtained in 10 children showed return of the initial state after about 3 weeks.

Pertussis

Salbutamol Combined with Erythromycin and Sobrerol in the Therapy of Pertussis (Italian)

V. Crosca, A. Ajello, C. Crosca and A. Minniti. Arch Sci Med (Torino) 1982 Apr-Jun;139(2):247-50.

English summary: The results of treatment carried out with salbutamol, erythromycin and fluidifiers in 20 children with whooping cough are reported. Results in all cases were much superior to those that have been obtained up to the present with the use of antibiotics alone or associated with hyperimmune gammaglobulins and/or sedatives. A speedier and more complete resolution of symptomatology was observed in the group where treatment was instituted earlier.

Parapertussis: An Abortive Pertussis Infection?

M. Granstrom and P. Askelof. Lancet 1982 Dec 4;2(8310):1249-50.

Authors' abstract: It is postulated that parapertussis and pertussis do not represent two distict infections but are both caused by *Bordetella pertussis. Bordetella parapertussis* would represent only a non-toxgenic strain of *B. pertussis*, the conversion to *B. parapertussis* being due to loss of a lysogenic bacteriophage. The answer to long-term immunity may lie in the development of non-toxic subunit pertussis vaccines which could bring about the parallel eradication of both infections.

Serological Diagnosis of Pertussis: IgM, IgA and IgG Antibodies Against *Bordetella pertussis* Measured by Enzyme-Linked Immunosorbent Assay (ELISA)

M.K. Viljanen, O. Ruuskanen, C. Granberg and T.T. Salmi. Scand J Infect Dis 1982;14(2):117-22.

Authors' abstract: IgM, IgA and IgG antibodies against *Bordetella pertussis* were measured by enzyme-linked immunosorbent assay (ELISA) with an ultrasonicate of formalin-killed bacteria (a mixture of strains 1, 2 and 1, 2, 3) as antigen and disposable polystyrene 9-cuvette blocks as the solid phase. The specificity properties of the assay were assessed by an inhibition technique. Of the microbes tested, only *B. parapertussis* was able to cause a significant inhibition. In addition, IgM and IgA antibodies against *B. pertussis* were only found in some sporadic cases of respiratory infections caused by other microbes. Sera, nasal swabs and cough plates were received from 198 patients with suspected whooping-cough. ELISA determinations were mostly made from only one serum sample of each patient. Paired sera were studied only from the culture-positive infants under 3 months of age. The number of positive cultures was highest in the group under 3 months of age (41%), where the frequency of positive ELISA was lowest (20%). The use of paired sera strikingly increased the number of ELISA-positive individuals in this youngest patient group. In later life, the relationship between these tests changed: isolation was positive in only about 10% of the patients, whereas 29-64% yielded positive titers in ELISA. This study shows that pertussis ELISA is a valuable aid in the rapid diagnosis of pertussis, particularly of the atypical forms of the disease which mostly are culture-negative.

Serologic Diagnosis of Pertussis: Comparison of Enzyme-Linked Immunosorbent Assay and Bacterial Agglutination

J. Mertsola, O. Ruuskanen, T. Kuronen and M.K. Viljanen. J Infect Dis 1983 Feb;147(2):252-7.

Authors' abstract: An enzyme-linked immunosorbent assay (ELISA) and bacterial agglutination (BA) method for determining the presence of antibodies to *Bordetella pertussis* were compared on serum samples from 21 patients with whooping cough and their 76 family members. The overall diagnostic agreement between the two methods was 77%. The data for BA-detected antibodies correlated best with IgG and IgA antibodies to *B. pertussis.* All of the culture-positive patients showed serologic positivity in both assays during the follow-up. Pertussis was diagnosed by ELISA in most cases from the first serum sample. Both methods proved to be good diagnostic aids in culture-negative patients, although the value of BA is more retrospective because of the need for paired sera. The kinetics of IgM, IgA, IgG, and agglutinating antibodies to *B. pertussis* is presented.

Purification and Characterization of a Fimbrial Hemagglutinin from *Bordetella pertussis* for Use in an Enzyme-Linked Immunosorbent Assay

P. Askelof, M. Granstrom, P. Gillenius and A.A. Lindberg. J Med Microbiol 1982 Feb;15(1):73-83.

Authors' abstract: The fimbrial hemagglutinin (F-HA) of *Bordetella pertussis* grown on solid medium was extracted with 1M sodium acetate for 72 hours at 20° C, and partially purified by Sephacryl S-300 gel chromatography. A pooled fraction with fimbrial hemagglutinating activity was shown to contain fimbriae of the expected morphology by electron microscopy. Chemical and biological assays showed that the F-HA fraction contained some heat-labile agglutinogen and lipopolysaccharide but no measurable lymphocytosis-promoting factor or heat-labile toxin. The F-HA fraction used as antigen in an enzyme-linked immunosorbent assay (ELISA) permitted the detection of antibodies in convalescent serum from a patient with whooping cough. The impurities, heat-labile agglutinogens and lipopolysaccharide, did not contribute to the ELISA activity. The method for preparation of the F-HA antigen is simple, reproducible and gives a high yield.

Detection of Antibodies in Human Serum Against the Fimbrial Hemagglutinin of *Bordetella pertussis* by Enzyme-Linked Immunosorbent Assay

M. Granstrom, A.A. Lindberg, P. Askelof and B. Hederstedt. J Med Microbiol 1982 Feb;15(1):85-96.

Authors' abstract: Antibody responses in human sera against *Bordetella pertussis* during natural infection were investigated by a microplate enzyme-linked immunosorbent assay (ELISA) with a purified fimbrial hemagglutinin preparation as antigen. Significant rises of specific IgG, IgM and IgA were demonstrated in paired sera. A secondary type of antibody response was found in most children and adults. In children, the type of response correlated with previous vaccination status; there was a primary response in unvaccinated children. A survey of antibodies in the general population showed low IgG titers in a small proportion of sera from the youngest healthy children. The titers and the number of individuals with measurable antibodies increased with age. In a limited study of the effect of vaccination, significant rises of titers were demonstrated after vaccination. The ELISA test was specific for antibodies against *B. pertussis* except that the test also seemed to measure antibody to *B. parapertussis.* A comparison between ELISA and the complement-fixation test showed a good correlation between the tests only in sera from children 1-12 years old.

Serologic Diagnosis of Whooping Cough by an Enzyme-Linked Immunosorbent Assay using Fimbrial Hemagglutinin as Antigen

M. Granstrom, G. Granstrom, A. Lindfors and P. Askelof. J Infect Dis 1982 Dec;146(6):741-5.

Authors' abstract: Diagnosis of whooping cough by an enzyme-linked immunosorbent assay (ELISA) that measures serum IgG, IgM, and IgA antibody to the fimbrial hemagglutinin of *Bordetella pertussis* was compared to isolation from nasopharyngeal swabs in a prospective study. Of 77 patients with upper respiratory tract infections of unknown etiology in which *B. pertussis* infection could not be excluded on clinical grounds, 26 were culture-positive, including one for *Bordetella parapertussis.* All 26 patients were positive by ELISA except one asymptomatic erythromycin-treated patient (ELISA sensitivity, 96%). Among culture-negative patients, 24 additional patients were positive by ELISA. Thus, only about one half of the patients with whooping cough were identified by culture under optimal conditions. Positive titers of IgM antibody and/or high titers of IgG antibody in the first serum sample, allowing for a rapid diagnosis, were found only in 26 (53%) of 49 serologically positive patients. By combining culture testing with serology, rapid diagnosis was obtained in 41 (82%) of 50 patients.

Pertussis Surveillance, 1979-1981

Anonymous. MMWR 1982 Jul 2;31(25):333-6.

In the 3-year period, 1979-1981, the Centers for Disease Control supplementary surveillance system received reports of 1,277 cases from 42 states. Analysis of the data from this supplementary system indicates that 62% of the cases involved children <1 year of age, and that 79% of these cases were among children <6 months of age.

Of 479 reported pertussis patients, ages 6 months—9 years, with known vaccination status, 33% were not vaccinated with DTP before becoming ill, and 60% had received <3 doses. Findings for the patients on whom clinical information was available showed that 72% had a whoop and 41% had apnea. Pneumonia was reported as a complication for 29% of patients. The frequency of pneumonia was highest (34%) among infants <6 months of age. For patients <4 years of age, the likelihood of pneumonia was inversely related to the number of DTP doses (for children 0—5 months, $p=0.009$; for children 6 months—4 years, $p=0.025$).

Seizures were reported for 51 (4%) of 1,277 patients; 29 (56%) of these patients were <6 months of age. Among patients <4 years of age, the likelihood of developing seizures was also inversely related to the number of DTP doses received; however, the difference was not statistically significant. Encephalopathy was associated with 0.4% of cases. All patients reported to have encephalopathy were <1 year of age.

Fifty-eight percent of all reported patients were hospitalized, including 80% of infants <6 months of age, 60% of those 6—11 months of age, and 35% of those 1-4 years of age. Relatively few patients >4 years of age were hospitalized. The proportion of patients hospitalized was inversely related to the number of doses of DTP vaccine received; the highest proportion of patients hospitalized occured among children who had received <3 doses of DTP vaccine ($p=0.0046$ for 6- to 11-month-olds and <0.0001 for 1- to 4-year-olds).

Vaccine efficacy for household contacts <5 years of age was 82.4%. Efficacy could not be calculated for children 5-9 years of age because very few household contacts in this age group were unvaccinated.

Spread of Whooping Cough Among Adults Today (Russian)

E.A. Okinshevich, L.A. Sigaeva, M.E. Sukhareva, M.S. Petrova and M.K. Naumova. Zh Mikrobiol Epidemiol Immunobiol 1982 Jan;(1):58-63.

English summary: Epidemiological surveys with the use of the clinical and bacteriological methods of examination were carried out in 107 foci of pertussis in families (283 adults), 25 foci in children's institutions (103 employees) and 1 focus in a surgical department for infants (29 adults). The infection was shown to be widely spread among adults at present: 23.7% in the surveyed families, 10% in children's institutions and 6.9% in the surgical department for infants. In the families, 26.2% of the adults were the first to fall ill with pertussis. No essential differences in the terms of the release of the infective agent, as well as in the course of the disease, in adults and in vaccinated children were found. Antiepidemic measures in respect to adult pertussis patients are proposed.

The Recurrence of Whooping Cough: Possible Implications for Assessment of Vaccine Efficacy

P.E. Fine and J.A. Clarkson. Lancet 1982 Mar 20;1(8273):666-9.

Authors' abstract: Though overall pertussis incidence fell in England and Wales subsequent to the introduction of vaccination on a national scale in the 1950s, pertussis epidemics have continued to occur regularly every 3-4 years. Since epidemic frequency is a function of the rate of influx of susceptibles, it is surprising that the interepidemic period did not decrease after the 1974 fall in vaccine uptake. One explanation for this paradox may be that pertussis vaccines are more effective in protecting against disease than in protecting against infection. This distinction should be considered in discussions of the efficacy of any vaccine.

Efficacy of Pertussis Vaccination in England. Report from the PHLS Epidemiological Research Laboratory and 21 Area Health Authorities

Anonymous. Br Med J [Clin Res] 1982 Jul 31;285(6338): 357-9.

Author's abstract: A national assessment of the efficacy of pertussis vaccination was made in 21 area health authorities in England. Notification rates for children given either three doses of diphtheria/tetanus/pertussis vaccine or diphtheria/tetanus vaccine were studied during the two and a half-year period January 1978—June 1980. A survey of home circumstances showed that the two vaccine groups could be validly compared. Home visits were made to assess the severity of the illness, the attack rates in home contacts, and to take pernasal swabs. Pertussis vaccination was found to be of outstanding value in preventing serious disease. Nevertheless, its effect in controlling whooping cough is limited by the fact that protection for home contacts is less satisfactory, and by the occurrence of mild cases in vaccinated children which may contribute to the spread of the disease.

Recent Findings from the 1970 Child Health and Education Study: Preliminary Communication

N.R. Butler, J. Golding, M. Haslum and S. Stewart-Brown. J R Soc Med 1982 Oct;75(10):781-4.

Authors' abstract: We describe the progress of a longitudinal cohort study based on all children born in England, Scotland and Wales in one week of April 1970. The children and their mothers have been surveyed at birth, at five, and recently, at ten. Analyses of the data presented include the finding of improved intellectual outcome in children who had been immunized against pertussis, compared with poor intellectual outcome in children who had had hospital admissions for the disease itself. Preliminary data collected at 10 years show that routine hearing and vision testing during the child's school life fell short of recommended standards. The major aim of the 10-year-old contact, however, is to establish details of the national prevalence and pathogenesis of disability. The identification of disability uses a life skills questionnaire, medical history and examination.

Evaluation of the Pertussis Components of Diphtheria-Tetanus-Pertussis Vaccine

M.D. Murphy, J. Rasnack, H.D. Dickson, M. Dietch and P.A. Brunell. Pediatrics 1983 Feb;71(2):200-5.

Authors' abstract: The adjuvant and antigen components of the pertussis fraction of diphtheria-tetanus-pertussis (DTP) vaccine were evaluated. Four preparations of DTP vaccine composed of either whole cell (Wc) or extracted (E) pertussis antigen combined with either an aluminum phosphate (Ph) or alum (Al) adjuvant were compared. Local reactions were similar in all four vaccines after the first two immunizations but were significantly increased in incidence and severity following the third immunization with vaccine WcPh. This appeared to be due to the Ph adjuvant rather than the antigen component. Febrile reactions were experienced more often ($p=.0009$) and with higher temperatures ($p=.0001$) with the WcPh vaccine following the first immunization. This appeared to be due to the Wc component. Comparing the pooled Wc groups with the pooled E groups revealed a greater febrile response in the Wc group after both the first ($p=.0008$) and the second ($p=.03$) immunization. Local reactions appear temporally and etiologically to be distinct from febrile reactions. The pooled Wc antigen group produced a higher geometric mean titer than the pooled E antigen group ($p=.05$). Serologic responses, with respect to geometric mean titer, were not significantly different among the individual vaccines. This study suggests that the combination of whole cell and aluminum phosphate, which is currently in use in the United States, is probably not the optimal formulation for pertussis vaccine.

Tetanus

Therapeutic Efficacy of Human Anti-Tetanic Globulin—A Clinical Study of 100 Cases

M.M. Bagree, J.D. Singh, D.L. Kanwar and R.C. Nagar. Jpn J Surg 1982;12(1):26-9.

Authors' abstract: The present study was performed to evaluate clinically the therapeutic efficacy of human anti-tetanic globulin in established cases of tetanus. The study was conducted in 100 patients in India with tetanus receiving treatment at P.B.M. Hospital, Bikaner. The human anti-tetanic globulin was given in addition to equine anti-tetanic serum, to all those patients who could afford to purchase the same, irrespective of age, sex or the severity of the disease, during the period of study. Except for the administration of human anti-tetanic globulin, the management of all the patients was identical. The study revealed that human anti-tetanic globulin is effective for patients with a short period of onset. Patients having prolonged spasms at frequent intervals were also the beneficiaries, to some extent. The hospitalization period of all the patients receiving human anti-tetanic globulin was shortened.

Intrathecal Anti-Tetanus Serum (ATS) and Parenteral Betamethasone in the Treatment of Tetanus

P.P. Thomas, E.B. Crowell, Jr. and M. Mathew. Trans R Soc Trop Med Hyg 1982;76(5):620-3.

Authors' abstract: 217 cases of tetanus admitted to Christian Medical College and Brown Memorial Hospital, Ludhiana, from June 1977 to April 1980 were studied. Three treatment regimes were used during this period. The addition of intrathecal horse antitetanus serum (ATS) (Group II) to the routine treatment (Group I) reduced the mortality from 63% to 53% but this was not statistically significant. Following a further addition of parenteral betamethasone to the regimen (Group III) the mortality decreased to 27% which was significantly lower than in Groups I and II. A similar trend in mortality was demonstrated when the severe cases were analyzed separately. Groups I and III were comparable in terms of various prognostic factors and the nursing care received but Group II had a higher incidence of unfavourable prognostic factors, which may have obscured the benefit of intrathecal ATS. The combination of parenteral betamethasone and intrathecal ATS seems to be beneficial in the treatment of tetanus.

Neonatal Tetanus—Long-Term Residual Handicaps

P. Teknetzi, S. Manios and V. Katsouyanopoulos. Arch Dis Child 1983 Jan;58(1):68-9.

Authors' abstract: Thirty-eight survivors of neonatal tetanus were assessed, 5 to 12 years after recovery, for neurological sequelae, physical growth, and maturation. Apart from appreciable handicaps (cerebral palsy, mental deficit, behavioral disturbances) in 4 cases, no harmful effect on physical growth or development was found. The fact that affected patients had frequent and prolonged bouts of spasms and apnea suggests that anoxia was the main cause of brain damage.

Detection of Antibodies to Tetanus Toxoid: Comparison of a Direct Hemagglutination Method with a Radioimmunoassay

A.S. Wang, G.F. Burns, I.J. Kronborg and I.R. Mackay. J Clin Pathol 1982 Oct;35(10):1138-41.

Authors' abstract: Two methods of detecting antibodies to tetanus toxoid were compared, a radioimmunoassay (RIA) employing radiolabelled staphylococcal protein A and a direct hemagglutination (HA) method employing sheep erythrocytes coupled to tetanus toxoid with chromic chloride. These were shown to have a similarly high specificity with the HA method showing slightly higher sensitivity. Hemagglutination offers several additional advantages in terms of simplicity, low cost and less requirement for specialized equipment. The assays were also used to demonstrate a transient IgM response after repeated booster injections with absorbed toxin given to seropositive individuals, and these antibodies were found to be protective in biological tests.

Use of Tetanus Toxoid for Testing Cell-Mediated Immunity

S. Whittingham, B. Feery and I.R. Mackay. Aust NZ J Med 1982 Oct;12(5):511-4.

Authors' abstract: Tetanus toxoid was assessed as a skin test antigen for the measurement of cutaneous delayed-type hypersensitivity (DTH) by comparing the responses to intradermal injections of aqueous tetanus toxoid and an extract of *Candida albicans* in 50 randomly selected healthy adults and 10 adults with immunodeficiency. Of 42 healthy subjects previously immunized with tetanus toxoid, 33 (79%) reacted to tetanus toxoid and 33 (79%) reacted to *Candida albicans.* Of eight non-immunized subjects, none reacted to tetanus toxoid although five reacted to *Candida albicans.* Ten immunodeficient adults previously shown to be anergic to a standard panel of five skin test antigens including *Candida albicans,* and who had received primary immunization and booster doses of tetanus toxoid, were anergic on current testing with tetanus toxoid and *Candida albicans.* Tetanus toxoid in previously immunized subjects has certain advantages as a "recall" DTH test antigen over the standard skin test antigens—candidin, mumps, trichophyton, tuberculin and streptokinase-streptodornase—used to diagnose cell-mediated immunodeficiency. It is a sensitive measurement of DTH, it recalls a defined immunological event, it has a low incidence of side effects, and it produces a slight but beneficial boosting of serum antibody to tetanus toxoid.

Naturally Acquired Antibodies to Tetanus Toxin in Humans and Animals from the Galapagos Islands

R. Veronesi, B. Bizzini, R. Focaccia, A.L. Coscina, C.C. Mazza, M.T. Focaccia, F. Carraro and M.N. Honningman. J Infect Dis 1983 Feb;147(2):308-11.

Authors' abstract: A serologic survey using a highly sensitive enzyme-linked immunosorbent assay confirmed the anticipated finding of naturally acquired antibodies to tetanus toxin both in humans and animals on the Galapagos Islands. In 57 inhabitants (mean age, 31.3 years) who had not been vaccinated against tetanus, antibody to tetanus toxin was detected in the blood in varying titers (geometric mean [reciprocal] titer [GMT], 0.015 international units [IU]/ml). In one individual the titer of antibody was greater than 12.5 IU/ml. Two individuals who had never been vaccinated against tetanus but who had reported having had clinical tetanus had titers of antibody to tetanus toxin of 0.02 IU/ml and 0.3 IU/ml, respectively. All nine of the animals studied showed antibody to tetanus toxin (GMT, 0.028 IU/ml).

Protective Human Hybridoma Antibody to Tetanus Toxin

F. Gigliotti and R.A. Insel. J Clin Invest 1982 Dec;70(6):1306-9.

Authors' abstract: Postimmunization human B lymphocytes and mouse myeloma cells were fused to produce interspecies hybridomas secreting human antibody of predefined specificity with an initial frequency comparable to intraspecies fusion. After 13 months in culture, one clone continued to secrete high titers of human IgG antitetanus toxin antibody. This antibody binds to the B fragment of tetanus toxin and protects mice against tetanus. The demonstration of in vivo protection with a human monoclonal antibody is an important first step towards the ultimate goal of human administration of monoclonal antibodies for the prevention and therapy of human infections.

Specific in Vivo and in Vitro Antibody Response to Tetanus Toxoid Immunization

W.B. Ershler, A.L. Moore and M.P. Hacker. Clin Exp Immunol 1982 Sep;49(3):552-8.

Authors' abstract: Booster immunization of normal individuals with soluble tetanus toxoid (TT) produced significant levels of plasma anti-tetanus IgG and IgM detectable by an enzyme linked immunosorbent assay (ELISA). Similar changes in circulating anti-TT antibody were found in mice following primary immunization. There was, however, no correlation observed between circulating anti-TT antibody response and the proliferative response of peripheral blood mononuclear cells exposed to soluble TT in the immunized individuals. The capacity of the peripheral blood mononuclear cells to produce specific anti-TT antibody in vitro was evaluated using a new microculture antibody synthesis enzyme-linked assay (MASELA). It was observed that the production of specific antibody in vitro correlated with the circulating anti-TT antibody level and not with the proliferative response. Peripheral blood mononuclear cells from these recently secondary immunized individuals produced greater specific anti-TT antibody when cultured in TT coated plastic wells than did controls. The potential utility of this technique in assessing response to immunization and basic immune competence is discussed.

Use of Tetanus Toxoid for the Prevention of Neonatal Tetanus. 1. Reduction of Neonatal Mortality by Immunization of Non-Pregnant and Pregnant Women in Rural Bangladesh

M. Rahman, L.C. Chen, J. Chakraborty, M. Yunus, A.I. Chowdhury, A.M. Sarder, S. Bhatia and G.T. Curlin. Bull WHO 1982;60(2):261-7.

Authors' abstract: An analysis of the live births between September 1978 and December 1979 in a rural epidemiological surveillance area of Bangladesh showed that for infants whose mother had received two tetanus injections 48-64 months prior to delivery, the neonatal mortality rate was 63.8 per 1000 live births compared with 78.3 per 1000 for infants whose mother did not receive tetanus immunization. Immunization of women with two tetanus injections during pregnancy reduced neonatal mortality rates to 42.8 per 1000, a reduction of 35.5 per 1000. Mortality on day 4-14 was reduced even more—by about 70%. One injection during pregnancy did not appear to provide protection against tetanus neonatorum.

Humoral and Cellular Immunity Following Antitetanus Vaccination in Malnourished and Malaria-Induced African Children. I. Study of the Antitetanus Antibody Response (French)

L. Monjour, F. Bourdillon, M. Schlumberger, M.T. Fayet, C. Michon, J.J. Ballet, E. Gouba and M. Gentilini. Bull WHO 1982;60(4):589-96.

English summary: Serum antibody levels were determined by specific radioimmunoassay in 414 children aged

1—3 years, 7—8 weeks after one or two injections of adsorbed tetanus toxoid (124 IU/ml). Studies in a small group of non-immunized children showed that the possibility of preimmunization antibodies being present in some individuals could be neglected in interpreting postimmunization data.

Overall, antibody levels were greater than 0.04 IU/ml in more than 99% of the children after one or two immunizations: however, two injections gave significantly higher values. In a small group of children antibody levels were still increasing up to 90 days after one injection. No difference in antibody level distribution was observed between well nourished and malnourished children defined by objective criteria. Antibody levels were higher among breast-fed children after one but not after two injections. No significant difference in antibody level was detected between malaria-infected and non-infected children.

Peripheral Neuropathy After Multiple Tetanus Toxoid Injections

L. Reinstein, J.M. Pargament and J.S. Goodman. Arch Phys Med Rehabil 1982 Jul;63(7):332-4.

Authors' abstract: This case documents the 14th reported patient with peripheral neuropathy following tetanus toxoid injection. A 33-year-old man developed profound mixed sensorimotor peripheral neuropathy after receiving 2 tetanus toxoid injections over a 5-month period. Periodic serial electromyographic and nerve conduction studies performed over 2 years suggested both segmental demyelination and axonal neuropathy. The patient experienced partial recovery. Analysis of this case and 13 others reported in the literature indicates that in almost all cases (85%), patients had received multiple tetanus toxoid injections. Also, it appears that a prolonged interval of 14 or more days between the tetanus toxoid injection and the onset of neurological symptoms is associated with a poorer prognosis for complete recovery.

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OTHER VACCINE-PREVENTABLE DISEASES

General

Infections in Pregnancy: Highlights from the Collaborative Perinatal Project

J.L. Sever. Teratology 1982 Apr;25(2):227-37.

Author's abstract: The longitudinal study of approximately 60,000 pregnant women was conducted at 14 major medical centers throughout the United States. Clinical data were obtained under prescribed protocols for each of the study women throughout their pregnancy, at delivery, and through the postpartum period. The children were followed with uniform examinations from birth through seven years of age. In addition, blood samples were taken from the pregnant women at registration, every two months through pregnancy, at delivery, and six weeks postpartum. Cord blood samples were also taken from the children during the last half of the study. We have used this material from the Collaborative Perinatal Project for the investigation of the role of infections in the production of damage to the fetus and newborn. The frequency of clinically recognizing infection during pregnancy was determined and geographic variation was demonstrated. Serological tests were used to document certain diseases. The frequency of confirmed clinical cases per 10,000 were: rubella, 8; rubeola, 0.6; mumps, 10; varicella-zoster, 5. The epidemiology and clinical findings associated with infections were studied using serological methods. This has provided data on the frequencies of infections such as cytomegalovirus, herpes simplex, mumps, rubeola, respiratory syncytial virus, and others. The study of abnormal pregnancies and matched controls is in progress using serological techniques. A number of specific studies have been reported on infections including rubella, neonatal meningitis, cytomegalovirus, maternal urinary tract infections, and toxoplasmosis. Further testing is now in progress employing more sophisticated laboratory methods and more complete data analysis.

Acute Encephalitis of Viral Origin

M.L. Koskiniemi and A. Vaheri. Scand J Infect Dis 1982;14(3):181-7.

Authors' abstract: Seventy-five patients with acute encephalitis of confirmed or suggestive viral or virus-like etiology showed a predominance of herpes simplex virus (HSV) as an etiological agent (13.3—32.0%) in all age groups without seasonal variation and increasing in number during years. Mumps, occurring mainly in female patients, was next in order and thereafter coxsackievirus B, varicella-zoster, and adenoviruses, followed by multiple coincident infections, and a large number of occasional agents. HSV seems to have displaced tick-borne encephalitis virus as the major cause of acute encephalitis in Finland. Pregnancy appeared to increase susceptibility to HSV encephalitis. The outcome was associated with the etiological agent in the first hand, HSV and nonviral microbes appeared unfavorable, but also with the clinical symptomatology, particularly altered consciousness, mental symptoms and focal neurological signs. The need for exact and rapid diagnosis in all cases of acute encephalitis is underlined in view of the possibility of specific therapy.

Genital Antibody Response to a Parenteral Gonococcal Pilus Vaccine

D. McChesney, E.C. Tramont, J.W. Boslego, J. Ciak, J. Sadoff and C.C. Brinton. Infect Immun 1982 Jun;36(3):1006-12.

Authors' abstract: A parenteral gonococcal pilus vaccine which has previously been shown to be safe and antigenic also results in the production of specific local genital antibody. All three major antibody classes were present in the local secretions, but immunoglobulin A predominated, a portion of which is dimeric 11S immunoglobulin A. This mucosal antibody is also capable of blocking the attachment of gonococci to epithelial cells. The antibody cross-reacted with five heterologous pili in a solid-phase radioimmunoassay. These results are encouraging and suggest that a gonococcal pilus vaccine may be efficacious in preventing gonorrhea.

Cholera

Is Cholera a Problem for U.S. Travelers?

J.D. Snyder and P.A. Blake. JAMA 1982 Apr 23;247(16):2268-9.

Authors' abstract: Only ten cases of cholera in U.S. travelers have been reported since the current cholera pandemic began in 1961. No important risk factors were apparent from assessing the age, place of acquisition, duration of mode of travel before infection, or history of cholera vaccination of the travelers who acquired cholera. All of the patients received medical treatment and all recovered; there were no secondary cases. Nine of the ten were infected by *Vibrio cholerae* 01 El Tor, the strain responsible for the current pandemic. Using the number of U.S. citizens returning to the United States by commercial air carrier from Asia, Africa, and Oceania to estimate the population at risk, we found that the chance of acquiring a reported case of cholera is less than one case per 500,000 returning travelers.

Epidemiology of Cholera in Travellers, and Conclusions for Vaccination Recommendations

H. Morger, R. Steffen and M. Schar. Br Med J [Clin Res] 1983 Jan 15;286(6360):184-6.

Authors' abstract: All cases of cholera imported to Europe and North America between 1975 and 1981 were reviewed to assess the danger of cholera for visitors to endemic areas. Data were obtained from the health authorities of the respective countries. From a total of 129 cases notified to the World Health Organization, detailed reports were obtained on 117 patients. Of these, 66 (56%) were immigrants, refugees, from endemic areas, or foreign workers returning from leave in their native countries. Only 51 (44%) were citizens of countries in Europe or North America. The incidence per journey for foreign travellers visiting Africa or Asia was about 1 in 500,000. Stay in hospital was always short, and fewer than 2% of patients died. In view of the minimal risk and lack of reliability of cholera vaccination, such protection is not indicated for ordinary tourists visiting developing countries.

Dental Caries

Immunization Against Dental Caries. A Review

A.H. Rogers. Aust Dent J 1982 Apr;27(2):81-5.

Author's abstract: An attempt has been made to review the current state of knowledge in relation to the production of a completely safe, effective vaccine against dental caries. Almost all research has focused upon *Streptococcus mutans* on the assumption that it is of prime etiological importance. In earlier studies, whole or broken cells of *S. mutans* were used to immunize experimental animals but, because of the possible harmful effects of impure vaccines, more recent attempts have been made to find a suitable immunogen from purified cell components of this organism. When this has been achieved, there still remain the problems of proving its safety and efficacy and of devising suitable immunization schedules whereby relatively long-lasting protection can be provided.

Haemophilus influenzae Infections

Age-Related Response to Two *Haemophilus influenzae* Type b Vaccines

D.J. Pincus, D. Morrison, C. Andrews, E. Lawrence, S.H. Sell and P.F. Wright. J Pediatr 1982 Feb;100(2): 197-201.

Authors' abstract: Two types of Hib vaccines were compared for efficacy and safety in 71 normal children in three age groups: 36 to 72 months, 15 to 18 months, and 6 to 8 months. One vaccine contained the Hib-specific capsular polysaccharide, PRP; the second vaccine contained PRP combined with pertussis vaccine, PRP-P. A third vaccine, DTP, was administered to a control group for each age. Anti-PRP antibody levels were greater after vaccination with PRP-P than after PRP in all three age groups. Immunoresponsiveness to both vaccines increased with age. A lower incidence of side effects was seen with both PRP (15%) and PRP-P (20%) than with DTP (56%). The results suggest that PRP-P is both well tolerated clinically and has greater immunogenicity than PRP.

Malaria

Prospects for the Development of Malaria Vaccines

W.H. Wernsdorfer. Bull WHO 1981;59(3):335-41.

Author's abstract: The collection of epidemiological data on malaria in man dates from the time of the discovery of the human-pathogenic plasmodia, and, in retrospect, many of these observations can be seen to have an immunological connotation. This circumstantial evidence of the immunological phenomena in malaria was obtained during the first quarter of this century through the analysis of parasitological, clinical, and epidemiological data. The second quarter brought confirmation of the existence of a variety of immune phenomena in the naturally infected host, and the development of a number of animal models which proved to be useful in immunological studies. Also during that period the first successful attempts at inducing immune protection in experimental hosts were recorded. This work was considerably expanded during the 1970s and culminated in the evidence of sterilizing protective immunity against homologous challenge in human subjects immunized with irradiated sporozoites of *Plasmodium falciparum* and *P. vivax.* The development of immunodiagnostic methods, including serological techniques, made rapid progress during the same period. Recently, the application of the cell-fusion (hybridoma) technique to malaria has made it possible to produce pure, monoclonal antibodies, some of which have proved to be protective. These monoclonal antibodies should be useful in the isolation of pure, specific antigens, and the use of gene cloning and recombinant DNA techniques seems to offer realistic prospects of success in mass production. Development in this area has gathered momentum rapidly and the fact that specialized industries are now interested in the production of malaria vaccines is evidence enough that such vaccines have moved into the sphere of possibility.

Progress in Malaria Vaccine Development

S. Cohen. Br Med Bull 1982;38(2):161-5.

From author's conclusion: The slow development and incomplete nature of naturally acquired immunity to malaria in man do not encourage a belief in the feasibility of vaccination procedures in this disease. Nevertheless, experimental vaccination against rodent, simian and human plasmodia has frequently induced far greater immunity than that engendered by the corresponding natural infection. This apparent contradiction can be ascribed to the fact that living plasmodia not only induced immunity, but also activate processes that favor parasite survival; inactivated parasites in appropriate antigenic form, on the other hand, can immunize without generating responses that promote parasite survival.

Of the many different vaccination procedures which have been evaluated experimentally, current interest is centered upon those that employ free forms of the plasmodium, namely sporozoites, erythrocytic merozoites and gametes. Each form of vaccine has been shown to induce effective, but strictly stage-specific, immunity in a variety of experimental host-parasite combinations. However, none of these can be regarded as a practical candidate for development of a vaccine against human malaria. The three forms of the plasmodium are currently available in amounts inadequate even for preliminary standardization and testing, far less for mass administration. Given the nature of currently available culture techniques, the production of these three stages in amounts adequate for vaccine development appears unlikely in the near future.

This difficulty has directed attention towards the analysis of antigens from each of the three extracellular plasmodial stages. Malaria parasites of each stage are extremely complex and the task of identifying and characterizing antigens from amongst the host of observed antigenic components has been greatly simplified by the advent of hybridoma techniques, which permit the in-vitro production of monoclonal antibodies of defined specificity. This method, only recently applied to the problem of antigenic analysis of malaria parasites, has already led to the identification of putative protective antigens on sporozoites, merozoites and gametes. With these advances it now appears feasible to isolate, or to produce by synthesis or recombinant DNA technology, specific protective antigens from defined stages of human malaria parasites for evaluation as vaccines.

Meningococcal Infections

Epidemic of Meningococcal Meningitis in Bamako, Mali: Epidemiological Features and Analysis of Vaccine Efficacy

N. Binkin and J. Band. Lancet 1982 Aug 7;2(8293): 315-8.

Authors' abstract: Many studies have demonstrated the efficacy of meningococcal vaccine in nonepidemic meningococcal meningitis, but few have examined its efficacy in epidemic conditions. The effects of the vaccine on the course of a meningococcal meningitis epidemic in Bamako, Mali, between January and April 1981, were studied. The vaccine was effective in limiting further spread of the epidemic. The attack rate among those who received vaccine was lower than that in the unvaccinated (0.7/10,000 vs 4.7/10,000), and the case-fatality rate among vaccinees in whom meningitis developed was lower than that of the unvaccinated. Routine vaccination against meningococcal meningitis in Africa may be impracticable owing to the cost, the relatively short duration of effectiveness, and the irregular occurrence of epidemics. Vaccination early in the course of an epidemic, however, appears to be a useful and practicable method of limiting the spread of disease.

Protection Against Group B *Neisseria meningitidis* Disease: Preparation of Soluble Protein and Protein-Polysaccharide Immunogens

C.E. Frasch and M.S. Peppler. Infect Immun 1982 Jul;37(1):271-80.

Authors' abstract: Although effective polysaccharide vaccines have been developed for meningococcal groups A, C, Y, and W135, the purified group B polysaccharide has proven to be nonimmunogenic. Earlier studies indicated that serotype 2 outer membrane protein vaccines induced bactericidal antibodies in animals and protected them from meningococcal challenge. However, a similar vaccine induced only low levels of antiprotein antibodies in both adults and children. Methods were therefore developed to produce more immunogenic serotype 2 protein vaccines. We found that, by growing the organism for 65 to 72 hours at 32° C, three to four times more outer membrane protein was released into the culture medium than could be extracted from overnight-grown cells. The outer membranes were therefore purified directly from the broth by ultrafiltration followed by ammonium sulfate precipitation. Most of the lipopolysaccharide was selectively removed from the membranes by treatment with the nonionic detergent Brij-96. The Brij-96 was then removed and the resulting vaccine was filter sterilized. Some vaccines were prepared by combining equal parts of detergent-treated membrane protein and high-molecular-weight group B polysaccharide producing highly soluble vaccines. These new vaccines were compared by using an enzyme-linked immunosorbent inhibition assay to an insoluble vaccine (E-06) found to be poorly immunogenic in humans. A human serum with serotype 2 specificity was used in the inhibition assay, and 5 micrograms of E-06 was required for 50% inhibition, whereas less than 1 microgram of the soluble vaccines was required. Addition of group B polysaccharide slightly increased the inhibitory capacity of the protein component.

Human Immune Response to Various Doses of Group Y and W135 Meningococcal Polysaccharide Vaccines

J.M. Griffiss, B.L. Brandt and D.D. Broud. Infect Immun 1982 Jul;37(1):205-8.

Authors' abstract: A divalent vaccine containing equal weights of *Neisseria meningitidis* group Y and group W135 capsular polysaccharides was inoculated subcutaneously into groups of 32 military recruit volunteers at doses of 10, 25, 50, and 100 micrograms in 10-microliter/microgram volumes. At 4 weeks, the two higher doses induced significantly greater binding antibody responses than did the two lower doses. Differences in response were not found between the two higher doses or between the two lower doses. An additional 32 volunteers received a dose of 25 micrograms in a 20-microliter/microgram volume. Binding antibody response to this vaccine did not differ from the response to doses of 10 and 25 micrograms in 10-microliter/microgram volumes. In contrast, bactericidal antibody responses did not differ among doses. Bactericidal antibody was induced in 100% of individuals with low ($>4 \log_2$) preexisting serum bactericidal activity, regardless of dose. Bactericidal antibody nonresponse was restricted to individuals with high preexisting serum bactericidal titers. The discrepant dose response between binding and bactericidal antibody resulted from the induction of nonlytic antibody by the higher doses. We conclude that there are no advantages to doses in excess of 5 micrograms of these two chemically similar polysaccharides for the target population of young adult military recruits.

Immunoglobulin M and G Antibody Responses and Persistence of These Antibodies in Adults After Vaccination with a Combined Meningococcal Group A and Group C Polysaccharide Vaccine

E.C. Beuvery, A.B. Leussink, R.W. Van Delft, R.H. Tiesjema and J. Nagel. Infect Immun 1982 Aug;37(2):579-85.

Authors' abstract: Adult volunteers were injected with a combined meningococcal group A and group C polysaccharide vaccine. Immunoglobulin M (IgM) and IgG antibody levels against both polysaccharides were measured in serum samples taken 14 days as well as 3 years after vaccination. For both group A and group C polysaccharides, the IgM and IgG antibody levels at 14 days postvaccination were positively related. The IgM-to-IgG antibody ratio at 14 days postvaccination was an indicator for the persistence of both IgM and IgG antibodies during the next 3 years; a high ratio meant a short persistence, whereas a low ratio was associated with a long persistence.

The Immunological Response to Polyvalent Meningococcal Vaccine in Bauchi State, Nigeria

I. Mohammed and M.M. Damisah. Trans R Soc Trop Med Hyg 1982;76(3):351-3.

Authors' abstract: The post-vaccination antibody response to both Group A and Group C meningococcal polysaccharide antigen was studied in 397 male and 359 female vaccinated persons aged between 4 and 40 years from Bauchi Town and neighboring villages in Nigeria. No difference in response was observed between the sexes. Highest antibody levels occurred in those aged between 13 and 28 years. Hemoglobin genotype did not affect response. Malnourished children had significantly lower mean IgG, IgA and IgM levels and the response to meningovaccine was also lower than in normal children.

Multiple Sclerosis

Intrathecal Synthesis of Antibodies to Diphtheria and Tetanus Toxoids in Multiple Sclerosis Patients

A. Salmi, M. Viljanen and M. Reunanen. J Neuroimmunol 1981 Sep;1(3):333-41.

Authors' abstract: Antibodies to diphtheria and tetanus toxoids were measured in 30 multiple sclerosis (MS) patients and 30 neurological control patients by enzyme-immunoassays. The frequency of antibody-positive patients and the titer distribution were similar in both groups. In spite of this, some MS patients had intrathecal antibody synthesis to these toxoids. The histories of these patients did not reveal any diseases caused by diphtheria or tetanus bacteria but they had been vaccinated 2-24 years before the first clinical symptoms of MS. The findings suggest that lymphocytes earlier committed to specific antibody synthesis outside the brain compartment could enter the brain before or after the clinical onset of MS.

A Study of Measles Virus and Canine Distemper Virus Antibodies, and of Childhood Infections in Multiple Sclerosis Patients and Controls

R. Haile, P. Smith, D. Read, D. Nassim, C. Warlow and W.C. Russell. J Neurol Sci 1982 Oct;56(1):1-10.

Authors' abstract: We investigated the levels of neutralizing antibodies to measles virus and canine distemper virus (CDV) in 72 multiple sclerosis patients (MS) and matched controls and also examined the frequency and age of onset of a number of childhood illnesses, including measles. The frequency of each childhood illness was not significantly different between cases and controls, but cases did report a later age at measles infection. Our data suggest that the risk of MS is increased by a factor of 1.9 if measles infection occurs between 5 and 9 years of age. A validity survey, based on a questionnaire to general practitioners, suggested substantial inaccuracy in the patients' reports of when they had measles, but the direction and degree of inaccuracy did not appear to be different between cases and controls. We also found higher titers of neutralizing antibodies in cases than controls to both measles virus and CDV, although the CDV difference was not statistically significant. In the light of a significant correlation between measles and CDV titers in both cases and controls, we used paired logistic regression to determine if the case-control difference in titers for each virus could be explained by a confounding effect on one by the other. The numbers were too small, however, to enable us to separate out any independent association of either virus with MS.

Mumps

The Increasing Incidence of Juvenile Onset Diabetes in the Baltimore Area: Lack of Correlation With Secular Incidence of Mumps

S.A. Chalew, J.A. Rappazzo, J.V. McLaughlin and N. MacLaren. Md State Med J 1982 Apr;31(4):67-70.

Authors' abstract: A retrospective study of juvenile onset diabetes (JDM) in patients aged 0-17 years was conducted in the Baltimore area for the period from 1960-1976. The incidence of new cases of JDM was found to be increasing among children 5-17 years of age. JDM incidence in the 0-4 years old had periodic fluctuation with a sharp decline after 1972.

No correlation was found between the incidence of JDM and the incidence of mumps, rubella, rubeola, or varicella. Factors influencing the rising incidence of JDM and qualitative differences between age groups remain to be clarified. A Maryland statewide registry for JDM would greatly aid investigation into the nature of these incidence trends.

Enzyme-Linked Immunosorbent Assay (ELISA) for Mumps Virus Antibodies

T. Popow-Kraupp. J Med Virol 1981;8(2):79-88.

Author's abstract: An ELISA for the detection of mumps virus-specific IgG and IgM antibodies was developed. Three different antigen preparations were compared. Equally good results were obtained with virus concentrated by ultracentrifugation and with virus that was further purified by sucrose gradient centrifugation. Crude infected allantoic fluid was unsuitable for use an antigen. The variability and reproducibility of the tests were satisfactory. When the ELISA was compared to conventional serological methods, a good correlation of IgG absorbance values with complement fixation (CF) antibody titers was found (r=0.574), the ELISA being more sensitive in detecting antibodies in acute-phase sera. For the determination of immunity, ELISA IgG values were compared with results obtained in hemagglutination-inhibition (HI) and hemolysis-in-gel (HIG) tests. Again there was a good correlation with both tests (rHI=0.528, rHIG=0.667). The ELISA was more sensitive than the HI and HIG test for the detection of low levels of antibodies.

Mumps-Specific Immunoglobulin M and G Antibodies in Natural Mumps Infection as Measured by Enzyme-Linked Immunosorbent Assay

P. Ukkonen, M.L. Granstrom and K. Penttinen. J Med Virol 1981;8(2):131-42.

Authors' abstract: An enzyme-linked immunosorbent assay for the demonstration of mumps immunoglobulin G (IgG ELISA) and immunoglobulin M antibodies (IgM ELISA) in serum was compared with complement fixation (CF), hemagglutination inhibition (HI), and hemolysis-in-gel (HIG) tests. The antibody levels measured by IgG ELISA had a high positive correlation with the CF and HIG tests, whereas only a moderate correlation was found between IgG ELISA and HI. Similar patterns of antibody response were observed with IgG ELISA, CF, and HIG: the antibody titers increased rapidly after the onset of symptoms and reached the maximal values in about three weeks. The HI antibodies developed more slowly during the first week of disease, after which the titers increased rapidly up to the fourth week. IgM antibodies measured by ELISA developed soon after onset of symptoms; most patients had IgM antibodies from the second day, and the highest titers were reached within the first week. The antibody response in mumps parotitis did not differ from that in mumps meningitis/encephalitis, while relatively higher antibody titers were found in patients with orchitis/epididymitis. The diagnostic efficiencies of the methods were compared with serum specimens from 33 patients who had a serologically verified mumps infection by at least one of the five methods used (rising antibody titers in paired sera or detectable IgM): IgM ELISA detected all 33 cases, IgG ELISA 29, HIG 28, HI 23, and CF 13. In 27 cases, IgM antibodies were already present in the acute phase serum specimens. It was concluded that mumps IgM ELISA is a more rapid and sensitive means for the serological diagnosis of mumps infection than the conventional tests.

A Benefit-Cost Analysis of Mumps Vaccine

J.P. Koplan and S.R. Preblud. Am J Dis Child 1982 Apr;136(4):362-4.

Authors' abstract: Applying benefit-cost analysis, we determined the savings in morbidity, mortality, and costs of mumps vaccination in the United States. Using reported mumps incidence rates in a model cohort of 1 million persons followed up for 30 years, mumps vaccination would prevent more than 74,000 cases of mumps and three deaths. Approximating the actual incidence rate of mumps, by assuming that 90% of people are infected by age 30 and 60% of these have had clinical illness, mumps vaccination would prevent more than 540,000 cases of mumps and 23 deaths. A mumps vaccination program, in which mumps was given as part of a measles-mumps-rubella combination, would reduce costs associated with mumps by more than 86%, with a benefit-cost ratio of 7.4:1, using reported incidence rates. The program has a benefit-cost ratio of 39:1 when approximations of actual mumps incidence are used in the analysis. Mumps vaccination is highly cost beneficial.

Antibody Response After Application of a New Live Attenuated Mumps Vaccine (Pariorix) Measured by Enzyme-Linked Immunosorbent Assay (ELISA)

T. Popow-Kraupp, C. Kunz and H. Hofmann. J Med Virol 1982;10(2):119-29.

Authors' abstract: Mumps virus specific antibody concentrations were determined by enzyme-linked immunosorbent assay (ELISA), hemolysis-in-gel (HIG) test, and hemagglutination-inhibition (HI) test in 17 adult volunteers before and after vaccination with a new live mumps vaccine, Pariorix. The results of the present study indicate that the strain Urabe-Am 9 of the mumps virus (Pariorix) induces antibodies in 100% of seronegative adults when measured by ELISA and in 70.6% and 64.7% in HIG and HI, respectively. ELISA is therefore a very sensitive and reliable method for the demonstration of seroconversion after vaccination. The vaccine was well tolerated and clinically acceptable in the group of adult volunteers.

Studies on Live Attenuated Mumps Vaccine. III. Long-Term Follow-Up Study on the Efficacy of Biken Vaccine

S. Isomura, M. Miyazu, H. Nagai, H. Naruse, M. Shibata, T. Ichikawa, S. Suzuki, K. Yamanishi and M. Takahashi. Biken J 1982 Jun;25(2):63-9.

Authors' abstract: Clinical and serological follow-ups were made on 24 children for 8 years after immunization against mumps with attenuated mumps vaccine, Biken vaccine. To evaluate the protective efficacy of the vaccine, matched controls were studied during the same period. Serological examination revealed that 91% of the controls were infected with mumps and 83% of them contracted the disease during the studied period. However, none of the vaccinees developed clinical infection after close contact with mumps patients. There was no substantial decrease in the antibody titers in unexposed vaccinees after vaccination.

Other Herpesvirus Infections

Immune Response to a DNA-Free Herpes Simplex Vaccine in Man

R. Cappel, S. Sprecher, F. Rickaert and F. de Cuyper. Arch Virol 1982;73(1):61-7.

Authors' abstract: A DNA-free subunit herpes simplex virus (HSV) vaccine was administered to 15 volunteers without past evidence of HSV infection and to 25 patients with severe recurrent HSV infection. The immune response to the vaccine in these patients was compared to the immunological status of 20 non-vaccinated control patients with recurrent HSV infection. The vaccine elicited antibody and cell-mediated immunity (CMI) in the 15 subjects without past evidence of HSV infection and this response was similar to that observed after a natural infection. Among the 25 patients who were suffering from recurrent HSV infection the vaccine elicited complement-dependent cytotoxic antibodies in 13 of these patients who did not possess these antibodies and increased significantly the titers of these antibodies in the 12 other patients. The vaccine gave a significant increase of the titers of the other specific antibodies as well as the level of cell-mediated immunity. The increase of the immunity level in these latter patients was not due to normal variations since in the non-vaccinated control group the antibody titers and CMI remained stable during the same period of time.

Pneumococcal Infections

Pneumococcal Infections and Pneumococcal Vaccine: An Update

M.W. Rytel. Infect Control 1982 Jul-Aug;3(4):295-8.

Author's abstract: Pneumococcal pneumonia continues to be an important disease in terms of prevalence, morbidity and mortality. With the discovery of penicillin and its wide clinical use, the overall mortality of pneumococcal pneumonia has been significantly reduced, but problems remain. These include: 1) death rate is uninfluenced by the antibiotic in the first five days of illness; 2) death rate in certain high risk groups and in patients infected with type 3 pneumococcus exceeds 25%; and 3) penicillin-resistant strains of pneumococci have emerged. Because of these and other considerations, a modern 14-valent pneumococcal vaccine has been developed by Robert Austrian and his co-workers. The vaccine has been found to be immunogenic and effective in a number of populations studied. Additional efficacy studies are needed, however, particularly in certain high risk groups, such as the elderly and immunocompromised patients.

Pneumococcal Disease in a Medium-Sized Community in the United States

M.A. Mufson, G. Oley and D. Hughey. JAMA 1982 Sep 24;248(12):1486-9.

Authors' abstract: To assess the importance of bacteremic pneumococcal disease among the population of one "average" American community, we studied all hospitalized patients who had *Streptococcus pneumoniae* isolated from blood, CSF, pleural fluid, or ascitic fluid during the years 1978 through 1981 in Huntington, West Virginia, and environs. Seventeen patients were children younger than 13 years, and 71 were adults. The case fatality rate from bacteremic pneumococcal disease among adults was 30%, and among children it was 6%. It was much higher (88%) in adults older than 50 years with extrapulmonary disease. Approximately four-fifths of the typed isolates from adults or children were types included in the current vaccine. Eighty-nine percent of the adults who died of pneumococcal infection had been candidates for pneumococcal vaccine, but only one patient had received vaccine, just before becoming ill with pneumococcal disease. These data provide a basis for widespread use of pneumococcal vaccine in high-risk groups.

Cost Effectiveness and Cost Benefit of Vaccination Against Pneumococcal Pneumonia: Implications for Clinical Practice

J.S. Willems. Infect Control 1982 Jul-Aug;3(4):299-302.

Author's abstract: The economic techniques of cost-effectiveness and cost-benefit analysis have provided useful insights into the potential advantages of vaccination against pneumococcal pneumonia. They suggest that the cost of vaccinating persons 65 years and older and perhaps younger persons with high risk conditions would be reasonable when compared with the cost of treatment for pneumococcal pneumonia. These findings, together with other considerations, may guide physicians and health care policymakers in deciding which individuals might be expected to benefit from pneumococcal vaccination.

Previous Hospital Care as a Risk Factor for Pneumonia. Implications for Immunization with Pneumococcal Vaccine

D.S. Fedson and J.A. Baldwin. JAMA 1982 Oct 22;248(16):1989-95.

Authors' abstract: In the Oxford Record Linkage Study population in 1970, seven hundred ninety-three persons were hospitalized for or died as a result of pneumonia. Thirty-six percent who survived and 49% who died had been discharged from hospital within the previous five years. For the period 1963 through 1970, cohort analysis determined the probability of subsequent readmission and/or death caused by pneumonia within the next five years for patients discharged with any condition and with high-risk conditions only. From this analysis, it was estimated that pneumococcal immunization of relatively few discharged patients would prevent each subsequent readmission and death from pneumococcal pneumonia. These results suggest that, in addition to age and underlying medical condition, patterns of previous hospital care can be used to identify many persons at increased risk of developing pneumonia. If current patterns of previous hospital care are similar to those found in Oxfordshire, physicians should consider giving pneumococcal vaccine to patients who are discharged from hospitals.

Pneumococcal Vaccination Practices Among Private Physicians

P.A. Patriarca, W.F. Schlech 3d, A.R. Hinman, J.M. Conn and W.J. Gunn. Public Health Rep 1982 Sep-Oct;97(5):406-8.

Authors' abstract: It is estimated that less than 10 percent of patients thought to be at high risk of invasive pneumococcal diseases have received 14-valent pneumococcal polysaccharide vaccine. To determine if any of these groups are more likely to be vaccinated than others, 893 private, primary-care physicians were surveyed nationwide. Although there was general agreement that the vaccine is indicated for the high-risk groups, patients with cardiorespiratory diseases were the only ones usually immunized by more than half of the survey respondents. The discrepancy between attitudes and practices could not be attributed to any specific factor.

Pneumococcal Vaccine: Clinical Efficacy and Effectiveness

J.S. Schwartz. Ann Intern Med 1982 Feb;96(2):208-20.

Authors' abstract: *Streptococcus pneumoniae* causes substantial morbidity and mortality. Incidence and severity are increased among populations with some chronic diseases. The currently available polyvalent polysaccharide vaccine induces antibody production among immunologically competent recipients against the 14 serotypes responsible for 80% of pneumococcal bacteremia in the United States. The vaccine is safe and has proved efficacious in clinical trials with healthy young men in epidemic conditions and in patients with sickle cell anemia. Similar trials in two other high-risk populations had inconclusive results. Decisions on vaccine use now largely rest on indirect evidence of efficacy derived from knowledge of disease incidence, severity, and antibody response to vaccination among patient groups. Findings of a literature review suggest vaccinating high-risk patients immunologically competent to produce homotypic antibodies in response to vaccination with polysaccharide antigen, while continuing investigation of disease incidence, severity, serotype distribution, and immunologic response among high-risk groups and postmarketing surveillance efforts among all vaccinated patients.

Pneumococcal Vaccine: Update and Evaluation

G.D. Overturf. Prog C[illegible] Biol Res 1982;98:59-71.

From author's summary [illegible] discussion: Splenic dysfunction accounts for the greatest deficiency of immune function of children with homozygous sickle cell disease. This dysfunction, coupled with the natural immunological immaturity of young children, subjects the young child with sickle cell disease to an immense risk of severe pneumococcal infections. The risk is greatest in the first three years of life but remains perceptibly greater than the normal population to well into adult life and probably continues life long. To date, experience would suggest that pneumococcal vaccine may provide only modest protection in the child with sickle cell disease less than five years of age. Poor antipneumococcal antibody production following immunization of children less than two years of age may be related to a developmentally determined failure of IgG-2 immunoglobulin production.

Nearly all reported failures of pneumococcal vaccine among children with sickle cell disease have occurred in children less than three years of age and frequently the offending pneumococci have been of serogroups 6, 23 and 14. Although vaccine is not totally efficacious in young children, it may provide some measure of protection against death and severe morbidity from pneumococcal infection in those children old enough to respond (i.e., those greater than three years of age). Therefore, its continued administration is strongly recommended in light of its mild side effects. Booster intervals have not yet been established for children with SCD, particularly young children. However, an interval of four to six years is probably adequate for children first immunized at greater than three years of age. Alternate prophylactic regimens have yet to be submitted to rigid scientific investigation and their utility in eliminating the risk of pneumococcal sepsis in the young asplenic child are, as yet, unknown.

Pneumococcal Polysaccharide Immunization of Children with Sickle Cell Disease. I. Clinical Reactions to Immunization and Relationship to Preimmunization Antibody

G.D. Overturf, J.G. Rigau-Perez, J. Selzer, R.J. Field, D. Powars, E.J. Pang, C. Uy, G. Honig, J. Weiss, L. Chan and B. Portnoy. Am J Pediatr Hematol Oncol 1982 Spring;4(1):19-23.

Authors' abstract: Vaccine reaction data were obtained from 154 patients with sickle cell disease immunized with tetradecavalent pneumococcal polysaccharide vaccine. There was a high rate (70%) of mild reactions, primarily at the site of injection. Fever over 100° F was uncommon and precipitation of symptoms similar to sickling crisis was rare. Development of local reactions was associated with the level of preimmunization pneumococcal antibody titer.

Pneumococcal Polysaccharide Immunization of Children with Sickle Cell Disease. II. Serologic Response and Pneumococcal Disease Following Immunization

G.D. Overturf, J.W. Selzer, L. Chan, J. Weiss, R. Field, J.G. Rigau-Perez, D. Powars, C. Uy, E.J. Pang, G. Honig, R. Steele, R. Edmonds and B. Portnoy. Am J Pediatr Hematol Oncol 1982 Spring;4(1):25-35.

Authors' abstract: One-hundred seventy-four children with sickle cell disease (SCD) were immunized with a single dose of tetradecavalent pneumococcal vaccine. Preimmunization and postimmunization antibody against 13 of the 14 pneumococcal capsular antigens was measured by indirect hemagglutination (IHA). The ability of each antigen to stimulate antibody following immunization was characterized by one of three types of responses: (1) poor antibody response regardless of the age at immunization (capsular types 6A, 14, and 19F); (2) improving antibody response with advancing age at immunization (capsular types 1, 4, 9N, 12F, 18C, and 23F): and (3) good antibody response regardless of age at immunization (capsular types 2, 3, 7F, and 8). An increase in antibody following immunization was significantly correlated ($p<0.0005$) with an increasing level of preimmunization antibody titer for all 13 antigens. Through the first 24 months of study, two episodes of pneumococcal sepsis caused by group 23 pneumococci were documented in two children immunized prior to 24 months of age (incidence rate, 4.40/100 patient-years in children <5 years of age), and one additional episode caused by a group 23 pneumococcus occurred in a 5 7/12-year-old child (incidence rate, 0.66/100 patient-years in children >5 years of age). These observations suggest that anamnestic immune response significantly contributed to the enhanced antibody response observed in older children and adults. Only modest vaccine efficacy may be expected among children with SCD who receive a single dose of pneumococcal vaccine.

Current Status of Pneumococcal Polysaccharide Immunization in Patients with Sickle Cell Disease or Impaired Splenic Function

A.J. Ammann. Am J Pediatr Hematol Oncol 1982 Fall;4(3):301-6.

Author's abstract: It is now possible to prevent effectively the occurrence of overwhelming pneumococcal infection from the majority of pneumococcal organisms in patients with increased susceptibility to infection. Immunization of patients with sickle cell disease and patients with splenectomy results in a significant increase in antibody amounts which persist for long periods of time. Patients under 2 years of age and patients with Hodgkin's disease and splenectomy respond less well. Most "vaccine failures" which have been described have been in immunosuppressed patients, or a result of infection with *S. pneumoniae* type 6A. Future directions in the development of a more effective vaccine for patients under 2 years of age and immunosuppressed patients will include research efforts to formulate a new immunogenic vaccine. Definitive recommendations regarding booster immunization must await more definitive studies, but current data suggest that booster immunization is not necessary for at least 5-6 years following primary immunization.

Adverse Reactions to Polyvalent Pneumococcal Vaccine

A. Ponka and M. Leinonen. Scand J Infect Dis 1982;14(1):67-71.

Authors' abstract: Adverse reactions to the polyvalent pneumococcal polysaccharide vaccine were evaluated with respect to age of the vaccinees and the route of administration. When either pneumococcal or influenza virus vaccine was administered by subcutaneous injection in a randomized single-blind study to 181 persons aged 60 to 85 years, local reactions were similar: one-third of the vaccinees complained of soreness at the injection site, whereas 90% had some local reaction (erythema, induration or soreness). Only 3/90 recipients of the pneumococcal vaccine and none of those who received the influenza vaccine had a slight rise in temperature (37.4—38.5° C). Most reactions subsided within 2 days. When the pneumococcal vaccine was given to 100 healthy firemen (mean age 31 years), local soreness was more common (76%) than among the old people ($p<0.001$), and fever was significantly more frequent (12%; $p<0.05$). Local soreness lasted somewhat longer after intramuscular (mean 42.5 hours) than after subcutaneous (mean 32.5 hours, $p<0.05$) injection, whereas local erythema was more common after subcutaneous (80%) than after intramuscular (38%) injection ($p<0.001$). The presence of reactions correlated with a higher concentration of antibodies to the vaccine polysaccharides.

Poliomyelitis

Late Progresive Muscular Atrophy and Antecedent Poliomyelitis

M. Alter, L.T. Kurland and C.A. Molgaard. Adv Neurol 1982;36:303-9.

From authors' introduction: Some patients with poliomyelitis seem to be "twice cursed," not only do they suffer muscle wasting from the initial viral illness, but an insidiously progressing muscular atrophy may develop many years later. The recrudescence of muscle atrophy has been called late-onset, post-poliomyelitis progressive muscular atrophy by Brooks et al. The disorder resembles amyotrophic lateral sclerosis (ALS) with progressive loss of muscle bulk, fasciculations of the tongue, and normal sensory findings. Nerve conduction is normal. Muscles already weakened by polio may be affected first, but in other cases, muscles apparently spared earlier are attacked. Pyramidal signs are less prominent than in classical ALS, and the course may be more prolonged. With both classical ALS and late progressive muscular atrophy more men are affected than women. [The possible association between progressive muscular atrophy and antecedent polio is discussed and the literature reviewed.]

Excretion of Attenuated Polioviruses in Children Vaccinated with Live Oral Poliovirus Vaccine

Z. Kucharska, H. Sramova and J. Zdrazilek. J Hyg Epidemiol Microbiol Immunol 1982;26(1):74-82

Authors' abstract: The excretion of attenuated polioviruses was studied in a group of nursery children vaccinated with 105TCD50 of each type of virus. The primovaccinated children were found to excrete type 1 poliovirus for 8 weeks, type 2 for 11 weeks after the vaccination with the type 1 + 2 bivaccine. Poliovirus type 1 was eliminated by 78% and type 2 by 98% of the vaccinees. The separately administered type 3 was detectable for 6 weeks and was isolated from 100% of the vaccinees. The highest percent of children with type 1 excretion positivity was recorded at week 5, with type 2 positivity at week 1 and with type 3 positivity at week 2. The poliovirus excretion peaked early after the vaccination, the titers of the poliovirus type 2 were the highest. The children revaccinated next year with the type 1 + 2 bivaccine eliminated the respective types of virus 1-2 weeks; type 3 poliovirus was detectable for 6 weeks after revaccination and was excreted by the highest percent of vaccinees. The contact infections caused by the attenuated polioviruses developed in 9 from 22 children vaccinated previously. The excretion of polioviruses did not last longer than 1 week. The contact infections were most frequently caused by the poliovirus type 2. The examined children, particularly those vaccinated previously, turned out to excrete also other enteroviruses identified as Coxsackieviruses B 4 and B 5 and Echovirus 21. In the primovaccinated, these viruses were isolated only from those with the negative excretion of polioviruses.

Alteration in Oligonucleotide Fingerprint Patterns of the Viral Genome in Poliovirus Type 2 Isolated from Paralytic Patients

T. Yoneyama, A. Hagiwara, M. Hara and H. Shimojo. Infect Immun 1982 Jul;37(1):46-53.

Authors' abstract: A close relationship was demonstrated by oligonucleotide fingerprinting between genomes of the poliovirus type 2 Sabin vaccine strain and recent isolates from paralytic cases associated with vaccination in Japan. The oligonucleotide maps of isolates from an agammaglobulinemic patient, who continued to excrete poliovirus type 2 for 3.5 years after the administration of oral vaccine, showed that the genomic alteration proceeded gradually, retaining the majority of the oligonucleotides characteristic of the vaccine strain for a long period, indicating vaccine origin for the isolates. The final isolate at month 41, however, lost the majority of these oligonucleotides. The heterologous antigenic relationship between the final isolate and the previous isolates was also observed. The serial alteration in electrophoretic mobility of the major structural proteins (VP1, VP2, and VP3) was observed throughout the excreting period. These results indicate that the population of the virus in this individual changed markedly during the last short period (about 3 months), in which the treatment with secretory immunoglobulin A was carried out. Genome comparisons in oligonucleotide maps show that some oligonucleotides in the genome of the vaccine strain are highly mutable after passage in humans.

Presence of Polioviruses and Other Enteral Viruses in Sewage: A Survey in the Czech Socialistic Republic, 1969-1976

J. Zdrazilek, M. Drasnar, H. Hlavova, E. Jadrnickova, L. Jandasek, V. Kasova, J. Koza, I. Matyasova, M. Uvizl, J. Valihrach and J. Weigendova. J Hyg Epidemiol Microbiol Immunol 1982;26(1):1-14.

Authors' abstract: Monitoring polioviruses in sewage is a permanent task within the poliomyelitis vaccination control program in Czechoslovakia. The results of sewage examination in certain localities of the CSR in the years 1969 to 1976 are reported. During the study years, nearly 3600 samples of sewage were examined. The yield was about 9 percent of samples positive for polioviruses and 22 percent of samples positive for other viruses. The virus positivity rate was roughly the same in samples from municipal sewers and samples from children's facilities. The majority of polioviruses were detected within 3 to 4 months after mass vaccination campaigns, which in Czechoslovakia are carried out in spring. In some years types 2 and 3 polioviruses tended to occur in later months after vaccination as well. Antigenic characterization of the polioviruses isolated in Prague showed that polioviruses possessing an rct+ marker and antigenically related but not identical with the original vaccine strains were sometimes present late during the intervals between vaccination campaigns. It may be assumed that vaccine strains which have been in circulation for a sufficiently long time are subject to a gradual change or that vaccine-like strains have been imported.

Poliomyelitis in the United States, 1969-1981

M. Moore, P. Katona, J.E. Kaplan, L.B. Schonberger and M.H. Hatch. J Infect Dis 1982 Oct;146(4):558-63.

Authors' abstract: During the 13-year period from January 1, 1969, to December 31, 1981, 203 cases of paralytic poliomyelitis were reported to the Division of Viral Diseases of the Centers for Disease Control (CDC), Atlanta. Most recently, 22 cases were reported in 1979, nine cases in 1980, and seven cases in 1981. These totals represent a dramatic decline since the early 1950s, when over 10,000 cases of paralytic disease were reported annually. Even during the very early years of the poliomyelitis vaccine era, several hundred to several thousand cases were reported each year. Since the 1950s, the attack rate of paralytic poliomyelitis has declined from a high of 13.7 cases per 100,000 population (1952) to 0.003 cases per 100,000 population (1981). As the number of cases declined, a changing epidemiologic pattern of occurrence of poliomyelitis in this country has been observed.

Prevalence of Antibodies to Poliovirus in 1978 Among Subjects Aged 0—88 Years

M. Roebuck and R. Chamberlain. Br Med J [Clin Res] 1982 Mar 6;284(6317):697-700.

Authors' abstract: The antibody state of a population aged 6 months to 88 years to poliovirus types 1, 2, and 3 was determined by examining 919 sera collected in Lancashire, London, and southern and southeast England. In subjects aged over 2 years the immune state was surprisingly uniform, although the older patients had probably acquired practically all their antibodies as a result of natural infection and those under 16 through vaccination. At least 95% had detectable antibodies to at least one poliovirus type and about 60% to all three types, with the exception of a cohort of children born between 1963 and 1968, in whom the proportions were about 80% and 40%, respectively. These children were born around the time of the changeover from inactivated to oral vaccine, when immunization rates were low and there was confusion over the number of doses required. These results indicate that a complete course of vaccine or a booster dose at or around school-leaving age is necessary.

Is Poliomyelitis a Serious Problem in Developing Countries? The Vellors Experience

T.K. John and T.J. John. J Trop Pediatr 1982 Feb;28(1): 11-3.

Authors' abstract: To assess the prevalence and incidence of poliomyelitis, we surveyed all children attending 66 schools in Vellore town in Tamil Nadu, India. Residual paralysis due to poliomyelitis (polio) was present in 110 among 34,112 school-going children, for prevalance rates of 4.1 per 1000 boys, 2.2 per 1000 girls, or 3.2 per 1000 children. The annual incidence was estimated to be 10 per 100,000 population. Calculated at this rate, at least 70,000 children develop polio each year, and about 2.24 million people are handicapped with polio in India. Thus it is a problem of considerable public health importance, and its prevention should receive high priority in India and other developing countries.

Eradication of Poliomyelitis in the United States

N. Nathanson. Rev Infect Dis 1982 Sep-Oct;4(5): 940-50.

Author's abstract: Mass immunization with oral poliovirus vaccine (OPV) was begun in the United States in 1963, and the last natural outbreak of poliomyelitis occurred in 1972. Since immunization programs fail to reach the total population, eradication has been achieved in the presence of a residual susceptible population of at least 5% (2—5 million children under the age of 15 years). It is proposed that the fade-out of wild polioviruses is explained by their disappearance during the winter, a low point in the yearly cycle of the virus. In the post-eradication era, the continued presence of millions of susceptible children and adults presents a constant potential hazard. Every effort should be made to maintain maximal levels of immunization with oral poliovirus vaccine and to prevent the reintroduction of wild polioviruses into the United States.

Vaccine Control of Poliomyelitis in the 1980's

A.B. Sabin. Yale J Biol Med 1982 May-Aug;55(3-4): 383-9.

Author's abstract: The main challenge of vaccine control of poliomyelitis in the 1980s is in the subtropical and tropical regions of the world where "lameness" surveys in recent years have shown how very high the average annual incidence of paralytic poliomyelitis can be in both rural and urban areas in the absence of epidemics. The procedures by which oral polio vaccine (OPV) rapidly eliminated all or almost all paralytic disease caused by polioviruses from the economically developed temperate climate countries have been inadequate in tropical and subtropical countries, except in some small countries with good health services, largely because there is much more year-round circulation of "wild" polioviruses which continue to produce the disease in the unvaccinated and incompletely vaccinated children. Not even a cheap, hypothetically 100 percent effective, one-dose vaccine could eliminate poliomyelitis in the tropics if, for a variety of reasons, it would reach only a portion of the infant population. Paralytic disease caused by polioviruses has been quickly eliminated from both small and large tropical countries by OPV in well-organized programs of annual mass vaccinations of almost all children under a certain age.

Immune Response of Infants in Tropics to Injectable Polio Vaccine

R. Krishnan, M. Jadhav, R. Selvakumar and T.J. John. Br Med J [Clin Res] 1982 Jan 16;284:164.

Authors' comment: Injectable polio vaccine is routinely used for infants and children in the Netherlands. The poliovirus antigen is formulated according to local needs and standards and contains relatively low levels of types 2 and 3. This is reflected in the seroresponse in our study. The response will probably improve further if the antigenic content of types 2 and 3 is enhanced.

This study suggests that the quadruple vaccine may be used in the routine immunization of infants in developing countries, starting as early as 6 weeks of age, with better antibody response than with oral polio vaccine. The seroconversion index after three doses of injectable polio vaccine given at four-weekly intervals was 94.1% whereas it was only 78% after three doses of oral polio vaccine given under similar conditions. If injectable polio vaccine could be manufactured in sufficient quantities and at an economic price, it would be an effective alternative to oral polio vaccine in tropical countries.

The Relation Between Acute Persisting Spinal Paralysis and Poliomyelitis Vaccine—Results of a Ten-Year Inquiry. WHO Consultative Group

Anonymous. Bull WHO 1982;60(2):231-42.

Author's summary: Most of the 13 countries that participated in this ten-year study of the incidence of acute persisting spinal paralysis (APSP) used trivalent live poliomyelitis vaccine (Sabin strains) but monovalent vaccines were used for all or part of the time in 3 countries and inactivated vaccines were used wholly by 2 countries and in part by 2 other countries. Altogether, 698 cases of APSP were recorded in a total population of about 509 million over the 10-year study period—an incidence of 0.14 per million per annum. The incidence varied widely between countries and not all the cases were related to immunization. In six countries where live vaccines were used, three methods of assessment of risk were employed. The risk in relation to the child population under 3 years of age was less than 1 per million children in all six countries.

In both vaccinees and contacts, most cases were due to poliovirus type 3; of those due to type 2, the proportion was greater among contacts than among recipients. Since the results make it clear that neurovirulence tests for safety do not prove the innocuity of a vaccine with absolute certainty, it is essential that every program of poliomyelitis immunization should include a continuous and effective system of surveillance. The study showed the need for the immunization of presumed susceptible adults at the same time as their children are vaccinated.

Though in most countries the incidence of vaccine-associated cases was low, two countries had much higher rates. In one the rate has now fallen but in the other it persists at the same level as before. No clear explanation of the differences between these and the other countries was obtained.

Rabies

A Comprehensive Rabies Control Program in Alaska

J. Middaugh and D. Ritter. Am J Public Health 1982 Apr;72(4):384-6.

Authors' abstract: In 1975 the State of Alaska initiated a comprehensive Rabies Control Program. Lay vaccinators trained and certified by the state provided animal vaccination in rural areas. From 1975 through 1980, 182 persons received post-exposure rabies prophylaxis with Human Rabies Immune Globulin (HRIG) plus Duck Embryo Vaccine (DEV), or Human Diploid Cell Vaccine (HDCV), while 2,569 persons initially thought to have been exposed were not treated after consultation, at a cost saving of approximately $3,220,241.

Human Diploid Cell Rabies Vaccine. Effectiveness of Immunization with Small Intradermal or Subcutaneous Doses

K.W. Bernard, M.A. Roberts, J. Sumner, W.G. Winkler, J. Mallonee, G.M. Baer and R. Chaney. JAMA 1982 Feb 26;247(8):1138-42.

Authors' abstract: To determine antibody responses to small doses of human diploid cell rabies vaccine (HDCV), we determined rabies antibody titers in 124 volunteers who had been vaccinated with one of five primary preexposure regimens. In a sixth group of 47 persons previously vaccinated with duck embryo rabies vaccine (DEV), we evaluated the booster responses after a 0.1-mL dose of intradermal (ID) HDCV. Persons in all five groups undergoing primary immunization received three doses of vaccine, one each on days 0, 7, and 28. The dose and route of vaccination for the five groups included 1 mL intramuscular (IM), 0.1 mL ID (two subgroups), 0.1 mL subcutaneous (SC), and 0.25 mL SC. Adequate titers developed in all persons, irrespective of the route or quantity of vaccine. The geometric mean titers (IU/mL) on day 49 in those receiving primary regimens were 12.87 (1.0 mL IM), 7.44 (0.1 mL ID by syringe), 3.05 (0.1 mL by jet injector), 3.17 (0.1 mL SC), and 6.47 (0.25 mL SC). Titers on day 90, while lower, were still acceptable. Adequate antibody titers developed in all persons previously vaccinated with DEV after a single 0.1-mL ID dose of HDCV; however, higher titers developed at day 7 in those who had shown an adequate response to DEV in the past. Results of this study suggest that HDCV may be used ID or SC for primary preexposure rabies prophylaxis and ID for booster immunization.

Intradermal Immunization with Human Diploid Cell Rabies Vaccine. Serological and Clinical Responses of Persons With and Without Prior Vaccination with Duck Embryo Vaccine

M.J. Burridge, G.M. Baer, J.W. Sumner and O. Sussman. JAMA 1982 Oct 1;248(13):1611-4.

Authors' abstract: Intradermal administration of human diploid cell rabies vaccine (HDCV) was investigated in an attempt to reduce the current high cost of preexposure rabies prophylaxis. The study population consisted of 240 volunteers from a veterinary hospital, 165 of whom had prior vaccination with duck embryo rabies vaccine (DEV). Vaccine safety was good; only minor reactions were experienced, all of which resolved spontaneously. Serological responses to intradermal HDCV were excellent; 209 (99.5%) of the 210 persons who completed the study produced rabies antibody titers of 0.50 IU/mL or greater (range, 0.50 to 40.00 IU/mL). Two 0.1-mL doses of HDCV given intradermally 28 days apart provide a safe, effective, and economical method for human preexposure prophylaxis against rabies, irrespective of the previous DEV vaccination history of the recipient.

Intradermal Use of Human Diploid Cell Vaccine for Preexposure Rabies Immunizations

D.W. Dreesen, J.W. Sumner, J. Brown and D.T. Kemp. J Am Vet Med Assoc 1982 Dec 15;181(12):1519-23.

Authors' abstract: In a study involving 240 faculty, students, and staff at the University of Georgia College of Veterinary Medicine, 0.1 ml of a rabies human diploid cell vaccine administered intradermally on days 0, 7, and 28 induced adequate rabies antibody (≥0.5 IU/ml of serum) in all subjects by day 49. There were no significant differences in mean titers between groups of individuals with different rabies immunization histories by using a newly proposed index system for reporting such titers. It was shown that if there was a titer on the day the initial dose was given, it had no bearing on the titer 49 days later. Less than 1% of all the injections resulted in severe reactions, i.e., muscular pain, headache, or pain at the site of injection. It was concluded that intradermal use of a low dose of rabies human diploid cell vaccine will induce adequate antibody titers in persons at risk to rabies.

Evaluation of a Human Diploid Cell Strain Rabies Vaccine: Final Report of a Three-Year Study of Pre-Exposure Immunization

G.S. Turner, K.G. Nicholson, D.A. Tyrrell and F.Y. Aoki. J Hyg (Lond) 1982 Aug;89(1):101-10.

Authors' abstract: The antibody responses of 194 volunteers were studied for up to 3 years after primary immunization with one, two or three doses of human diploid cell rabies vaccine, administered either in 0.1 ml volumes intradermally (i.d.) or as 1.0 ml intramuscularly (i.m.). Seroconversion occurred in 95% of subjects after the first injection and in 100% after the second. The highest titers and most durable antibody responses were induced by three injections of vaccine. Booster doses were administered either by the subcutaneous (s.c.) or i.d. route, after 6, 12 or 24 months to randomly grouped volunteers; these induced responses ≥5.0 i.u. per ml in 95% of subjects. The responses were rapid and were influenced neither by the primary regimen nor by the timing and route of the booster dose. Antibody titers after i.d. immunization were only two-fold lower than those induced by the larger volume of vaccine. The findings suggest that the i.d. route is both effective and economic.

Smallpox and Vaccinia

The Global Eradication of Smallpox

M.A. Strassburg. Am J Infect Control 1982 May;10(2):53-9.

Author's abstract: On May 8, 1980, the 33rd World Health Assembly declared the world free of smallpox. This followed approximately 2 1/2 years after the last documented naturally occurring case of smallpox was diagnosed in a hospital worker in Merca, Somalia. A major breakthrough for the eventual control of this disease was the discovery of an effective vaccine by Edward Jenner in 1796. In 1966 the World Health Assembly voted a special budget to eliminate smallpox from the world. At that time, smallpox was endemic in more than 30 countries. Mass vaccination programs were successful in many Western countries; however, a different approach was taken in developing countries. This approach was known as surveillance and containment. Surveillance was aided by extensive house-to-house searches and rewards offered for persons reporting smallpox cases. Containment measures included ring vaccination and isolation of cases and contacts. Hospitals played a major role in transmission in a number of smallpox outbreaks. The World Health Organization is currently supporting several control programs and has not singled out another disease for eradication. The lessons learned from the smallpox campaign can be readily applied to other public health programs.

A Successful Eradication Campaign. Global Eradication of Smallpox

F. Fenner. Rev Infect Dis 1982 Sep-Oct;4(5):916-30.

Author's abstract: Smallpox was the first important disease to be eradicated; it was the success of the Smallpox Eradication Program that inspired this conference. Several biological reasons favored the eradication of smallpox, the most important of which were probably that recurrent infectivity did not occur, that there was no animal reservoir, and that an effective stable vaccine was available. The importance of smallpox as a disease that travelers might import into countries free of smallpox provided a powerful stimulus for its global eradication. This paper highlights some of the problems associated with the eradication of smallpox in two countries where eradication was difficult, India and Ethiopia, and the measures adopted to overcome the problems. The paper also stresses the importance of the development of methods for the certification of smallpox eradication from countries, from regions, and finally from the whole world. It is noted that close links between field work and research were important throughout the eradication campaign.

Surveillance of Orthopoxvirus Infections, and Associated Research, in the Period After Smallpox Eradication

I. Arita and A. Gromyko. Bull WHO 1982;60(3):367-75.

Authors' abstract: In 1980, the World Health Assembly declared the global eradication of smallpox and recommended the universal discontinuation of smallpox vaccination; nevertheless, it recommended that surveillance and research on orthopoxvirus infections should continue. By early 1982, all except 8 countries in the world had stopped routine vaccination programs and all except 1 no longer required an international certificate of smallpox vaccination for travellers. Since 1978, as a result of continuing active surveillance, 176 smallpox rumors have been investigated in 60 countries. Two of these concerned the two laboratory-associated cases that occurred in the United Kingdom in 1978; all the others were false alarms. Special surveillance programs for human monkeypox have been developed in West and Central Africa. The number of laboratories retaining variola virus stocks has been reduced to four. Investigations to determine the identity and origin of the six known isolates of "whitepox" virus have continued. Research on mapping of variola DNA and on monoclonal antibodies against certain orthopoxvirus antigens is continuing. All these measures are aimed at ensuring that the achievement of smallpox eradication is permanent.

Recurrent Herpes Simplex Infection at a Smallpox Vaccination Site

L. Mintz. JAMA 1982 May 21;247(19):2704-5.

Author's abstract: A patient who received smallpox vaccinations to treat a recurrent genital herpes simplex virus infection had development of recurrent herpes at the vaccination site while his genital lesions continued unabated. Until smallpox vaccine is removed from the general market or reclassified as a restricted biological, the inappropriate use of this agent will continue.

Subacute Sclerosing Panencephalitis

Inosiplex Therapy in Subacute Sclerosing Panencephalitis. A Multicenter, Non-Randomized Study in 98 Patients

C.E. Jones, P.R. Dyken, P.R. Huttenlocher, J.T. Jabbour and K.W. Maxwell. Lancet 1982 May 8;1(8280):1034-7.

Authors' abstract: Inosiplex was administered to 98 patients with subacute sclerosing panencephalitis (SSPE) in the United States and Canada for variable periods of time up to 9.5 years. Survival data from these 98 patients were compared by life-table analysis with survival in three SSPE control groups drawn from SSPE patients contracting the disease in Israel, Lebanon, or the United States at about the same time as the inosiplex-treated patients but treated differently or not at all. In the inosiplex-treated patients the actuarial probability of survival at 2, 4, 6, and 8 years from onset of SSPE was 78%, 69%, 65%, and 61%, compared with 38%, 20%, 14%, and 8% in a composite control group ($p < 0.01$ for all four comparisons). Statistical adjustments for time-to-treatment bias did not affect this result: a modified logrank procedure demonstrated that the risk of dying in the treatment group was 43% of that in the controls. Inosiplex seems to be able to prolong life in patients with SSPE.

Long-Term Follow-Up of Patients with Subacute Sclerosing Panencephalitis Treated with Inosiplex

P.R. Dyken, A. Swift and R.H. DuRant. Ann Neurol 1982 Apr;11(4):359-64.

Authors' abstract: During the past five years, 15 patients with subacute sclerosing panencephalitis (SSPE) were treated with inosiplex. Using a disability index specifically designed for the disease, this study monitored the course of SSPE in each patient before and during inosiplex therapy. Posttreatment follow-up ranged from 2 to 144 months. Inosiplex had an apparently beneficial effect on morbidity and mortality in 10 of the 15 patients tested. Eight improved immediately after treatment, 2 had a delayed improvement, and 1 patient stabilized. Four patients followed a typical course for SSPE and died a mean 9 months after onset. Treatment was not associated with adverse reactions. Due to its low risk-benefit ratio, inosiplex is recommended for continuous use in SSPE even after extended remissions.

The Influence of Inosiplex Treatment on the Neurological Disability of Patients with Subacute Sclerosing Panencephalitis

R.H. DuRant, P.R. Dyken and A.V. Swift. J Pediatr 1982 Aug;101(2):288-93.

Authors' abstract. Subacute sclerosing panencephalitis is a central nervous system degenerative disease that rapidly progresses to death in most untreated cases. In this study we compare the level of neurological disability (ND) longitudinally in a group of SSPE patients receiving inosiplex (Isoprinosine) treatment (12) to a historical control group of untreated patients (15). The mean ND did not differ between the groups from onset of SSPE through 21 months. From two years through four and one-half years the inosiplex group had significantly lower ND compared to the nontreatment group. The subjects were then divided into four subgroups. Group 1, rapidly progressing SSPE, not treated; Group 2, slowly progressing SSPE, not treated; Group 3, rapidly progressing SSPE, inosiplex treated; and Group 4 slowly progressing SSPE, inosiplex treated. The rapidly developing groups did not differ in ND at any time. The slowly developing treated group had significantly lower ND than the slowly developing untreated group from two and one-half years to four and one-half years after onset of SSPE. These findings suggest that inosiplex is effective in the slowly developing or chronic form of SSPE.

Antibody Response to Structural Proteins of Measles Virus in Patients with Natural Measles and Subacute Sclerosing Panencephalitis

T.A. Sato, M. Hayami and K. Yamanouchi. Jpn J Med Sci Biol 1981 Dec;34(6):365-73.

Authors' abstract: By immunoprecipitation and SDS-polyacrylamide gel electrophoresis, antibody responses to the structural proteins of measles virus were examined on patients with various forms of natural measles, atypical measles, and subacute sclerosing panencephalitis (SSPE). The serum of atypical measles most strongly reacted with four structural proteins, i.e., hemagglutinin (H), nucleocapsid (NC), fusion (F), and matrix (M) proteins. In natural measles, antibodies to the four structural proteins were detected at such an early convalescent stage as one month after the onset of disease. In late convalescent serums taken 9 years after natural measles, however, only low level antibody to M protein was present, whereas antibodies to H, NC and F proteins persisted. The serums and cerebrospinal fluid of SSPE patients showed patterns similar with those of the late convalescent serums. In Vero cells infected with cell-associated SSPE viruses (Niigata-1, ZH, and SI strains), M protein was not clearly demonstrated with serum of either atypical measles or SSPE patients, whereas H protein was demonstrated.

Subacute Sclerosing Panencephalitis Antibodies Against Measles Virus Polypeptides

D. Karcher, H. Thormar, A. Lowenthal and M. Noppe. J Neurol 1982;227(1):29-34.

Authors' abstract. Antibodies to measles virus proteins in SSPE, MS and control human sera were compared using measles virus strain Edmonston, productive SSPE strain Mantooth and non-productive SSPE strain DR. The viral antigens were subjected to transfer electrophoresis, incubated with sera and localized after a second incubation with peroxidase labeled immunoglobulins. High levels of antibodies to all measles viral proteins are present in SSPE sera and CSF and to a lesser degree in MS and control sera although the non-productive SSPE strains lack one viral protein (M protein) present in wild type measles virus strains and the productive SSPE strains.

Measles Antibodies in the Saliva of Children with Subacute Sclerosing Panencephalitis

W. Sobczyk, I. Polna, J. Kulczycki and H. Horbowska. J Neurol 1982;228(3):219-22.

Authors' abstract: Using the method of hemagglutination inhibition, the authors determined the levels of measles antibodies in the saliva of 14 children with subacute sclerosing panencephalitis. In 13 of them, these antibodies were found in titers from 1:8 to 1:128. In the control groups, comprising 29 children, these antibodies were found in the saliva in only two cases and in low titers. There appears to be a correlation between the levels of these antibodies in the saliva and cerebrospinal fluid in patients with subacute sclerosing panencephalitis.

Distribution of Measles Antigen and Immunoglobulin-Containing Cells in the CNS in Subacute Sclerosing Panencephalitis (SSPE) and Atypical Measles Encephalitis

M.M. Esiri, D.R. Oppenheimer, B. Brownell and M. Haire. J Neurol Sci 1982 Jan;53(1):29-43.

Authors' abstract: The immunoperoxidase technique has been used to study the distribution of measles virus antigen and immunoglobulin (Ig)-containing cells within the CNS, in 5 cases of subacute sclerosing panencephalitis (SSPE) and 1 case of atypical measles encephalitis. Measles virus antigen was demonstrated within the brain in all cases, and in the spinal cord in 1 case of SSPE. Ig-containing cells were also demonstrated in all cases, the proportions of the different light and heavy chain types varying somewhat from case to case. In SSPE, IgG constituted the major and IgA the principal minor heavy chain demonstrated. In all cases of SSPE there was significant excess of light-chain-containing over heavy-chain-containing cells. In the case of atypical measles encephalitis there was a paucity of Ig-containing cells and a relatively high proportion (39%) of these contained IgM. The case of atypical measles encephalitis differed from those of SSPE also in the presence of multinucleate giant cells, some of which contained measles virus antigen.

Subacute Sclerosing Panencephalitis after Passive Immunization and Natural Measles Infection: Role of Antibody in Persistence of Measles Virus

K.W. Rammohan, H.F. McFarland and D.E. McFarlin. Neurology (NY) 1982 Apr;32(4):390-4.

Authors' abstract: Subacute sclerosing panencephalitis (SSPE) developed in a patient in whom natural measles infection was anteceded by immunization with measles immune serum globulin (ISG). This observation prompted experimental studies of the role of antibody in viral persistence. When Balb/c mice were infected with the hamster neurotropic measles virus, acute encephalopathy was fatal in 80% of the animals. When measles antibody was administered 3 days after virus inoculation, the acute disease was abolished and subacute encephalitis had a 30% mortality. The subacute disease was characterized by the presence of neuronal viral antigen, meningitis, and encephalitis. Induction of viral persistence was therefore a consequence of antibody transfer during viral infection. Caution is advised in human prophylaxis with immune globulin.

HLA Antigens in Subacute Sclerosing Panencephalitis

S. Aysun, F. Ersoy, O. Sanal, K. Yalaz, E. Ozdirim, A.I. Berkel and Y. Renda. Arch Neurol 1983 Jan;40(1):38-9.

Authors' abstract: A microlymphocytotoxicity test determined serologically the frequency of HLA antigens in 24 patients with subacute sclerosing panencephalitis (SSPE) and in 300 healthy control subjects. The results demonstrated no association between SSPE and the HLA-A and HLA-B antigens.

Tuberculosis

Selective Primary Health Care: Strategies for Control of Disease in the Developing World. II. Tuberculosis

T.M. Daniel. Rev Infect Dis 1982 Nov-Dec: 4(6):1254-65.

Author's abstract: Tuberculosis remains a major public health problem throughout the world. Practically all adults in developing countries are infected with the organism *Mycobacterium tuberculosis*, but only about five percent suffer any ill effects. Morbidity and mortality are greatest during the economically and socially productive young adult years. Treatment requires multiple drugs and many months of compliance. Treatment both reduces transmission of the organism and allays suffering in the diseased individual. The efficacy of vaccination with BCG (bacille Calmette-Guerin) remains controversial, but several trials have demonstrated some reduction in clinical disease. At this point, the ideal disease control program entails several steps of epidemiologic assessment of the problem and resources, development of public health orientation in the professional community, treatment of infectious patients, and BCG vaccination of all those under 15-20 years of age.

Tuberculosis in Children as an Important Indicator in the Fight Against Tuberculosis (Romanian)

I. Rogoz, D. Zaharia and I. Georgescu. Rev Ig [Pneumoftiziol] 1982 Jul-Sep:31(3):195-9.

English summary: In spite of the fact that tuberculosis in children is continuously declining (in the Brasov District it fell from 197 cases during 1960-1970 to 67 between 1977 and 1979), a large number of cases are still recorded in children under the age of 3 years (from a percentage of 23 of the total number of sick children in 1969 to 44.8 in the last period). Epidemiologic studies discovered infection sources in 91% of the vaccinated children (parents represented 68% of all sources). Thus, a familial or proximate source, detectable through this epidemiologic investigation, overwhelmed the protection provided by the BCG vaccination, which provided better protection against the more rare and sporadic extra-familial infections. It appears that in tuberculosis environments, BCG vaccination alone is less efficient and a more prompt application of other preventive measures should be considered, such as early detection, rapid removal of the source, or removing the children from the infective environment. Consideration should also be given to tuberculosis control in parents, especially fathers, who appear to be the source of infection twice as frequently as mothers.

Post-Vaccination Tuberculin Sensitivity for Assessing BCG Vaccination in Areas with High Prevalence of Non-Specific Sensitivity

R. Narain, R.S. Vallishayee and S. Mayurnath. Tubercle 1981 Dec:62(4):231-9.

Authors' abstract: The relationship of non-specific sensitivity to post-vaccination tuberculin sensitivity has been the subject of controversy. This relationship has an important bearing on the common practice of using post-vaccination tuberculin sensitivity for assessing BCG vaccination in areas with a high prevalence of non-specific sensitivity. If post-vaccination tuberculin sensitivity is found to be dependent on the amount of already existing, naturally acquired, non-specific sensitivity it could not be considered a reliable measure of the success of BCG vaccination. In a recent BCG trial in India a large number of persons were tested with PPD-S and PPD-B and also vaccinated with BCG vaccine or injected with placebo, by random allocation. Mutually exclusive random samples of the study population were retested with PPD-S at 2 1/2 months, 2 1/2 years and 4 years after vaccination. At each post-vaccination test the tuberculin sensitivity obtained among the placebo-injected controls provided a measure of the tuberculin sensitivity due to non-specific sensitivity that would have been present in the absence of BCG vaccination. The difference between the mean size of reactions to the post-vaccination test among the vaccinated and among the unvaccinated controls provided a measure of tuberculin sensitivity that was wholly due to BCG vaccination. Thus it was possible to separate and study the two components of post-vaccination tuberculin sensitivity. The results of the study indicate that post-vaccination tuberculin sensitivity can be used to assess BCG vaccination in areas with a high prevalence of non-

specific sensitivity, provided the assessment is done in younger age groups and based on post-vaccination tuberculin sensitivity as measured at 2-3 months after vaccination and not later.

Retrospective Assessment of the Effectiveness of BCG Vaccination Against Tuberculosis Using the Case-Control Method

P.G. Smith. Tubercle 1982 Mar;63(1):23-35.

Author's abstract: It is proposed that case-control studies might be used to assess the effect on the incidence of tuberculosis of the mass BCG vaccination campaigns that were conducted in many countries in Africa and Asia from the 1950s onwards. The cost of such studies would be relatively small and they could be completed within a year or two. The results would assist countries in planning their future strategies for tuberculosis control and information on the variation in the protective effect of BCG in a number of different areas in less developed countries may give clues to the reasons for such variation. It is suggested that case-control studies should be designed to include about 200 cases and 3 or 4 times as many controls. The cases should be selected for age such that at the time of the mass vaccination campaign they will have been in an age group in which 20% or less were tuberculin positive. The same approach may be used to assess the effectiveness of giving BCG at birth, provided that this policy has been adopted for some years, coverage has been good (about 50% to 80%) and there are reasonable facilities for diagnosing tuberculosis in children.

Pathogenesis of Tuberculosis and Effectiveness of BCG Vaccination

H.G. ten Dam and A. Pio. Tubercle 1982 Sep;63(3): 225-33.

Authors' abstract: Among the hypotheses offered to explain the conflicting results of various trials of BCG vaccination, the one invoking gross differences in the immunogenic properties of the various BCG vaccines (strains) has received most attention. Indeed, for many years research in BCG vaccination has been directed almost entirely towards improving the quality of vaccines. The anticipated benefit of this work, however, is not borne out by the results of the latest trial in India. Whereas it cannot be excluded that technological advances may have resulted in the worst vaccines ever, it also remains possible that the basic hypothesis was less relevant than presumed. The quality of the vaccine may be of little importance and a different explanation should be sought for the observed differences in protection. One possible lead is the observation that BCG vaccination consistently appeared to be of poor efficacy under conditions where, in a vaccination program, even an effective vaccine would have little impact on the tuberculosis problem, i.e., where the majority of cases originated from the population already infected. The hypothesis offered is that in such populations the pathogenesis of tuberculosis is different from that prevailing under the clearly exceptional conditions under which BCG vaccination was effective. Rather than being the direct result of primary infection, tuberculous disease (observed) may be the result of reinfection. In this case BCG vaccination cannot be expected to have a protective effect.

Osteitis and Other Complications Caused by Generalized BCG-itis. Experiences in Sweden

M. Bottiger, V. Romanus, C. de Verdier and G Boman. Acta Paediatr Scand 1982 May;71(3):471-8.

Authors' abstract: In 1973 an increase in the number of osteitis caused by BCG vaccination in the neonatal period was observed in Sweden. A high incidence of this complication, i.e., 1 case per 3000 vaccinated newborn children continued until this vaccination was interruped in 1975. In the years 1972 to 1980, a total of 90 cases were reported to the Adverse Drug Reaction Committee. Earlier retrospective studies had disclosed 36 cases born between 1949-1968 and an active search for unreported cases in the 1970s revealed an additional 26 cases. Of the total of 152 known cases in Sweden, 82 were boys and 70 girls. The mean incubation period was 14 months for boys and 23 for girls. Extremely long incubation periods were seen, i.e., 6 years in two children and 12 years in one. Eleven children had mutiple osteitis lesions. The epiphyses of the long bones of the extremities were the most frequent sites of the affection (109 lesions). The spine, which is the common site of osteitis caused by tuberculosis, was affected in only 6 patients. Relapses occured in two patients.

Varicella-Zoster Infections

A Cluster of Cases of Reye Syndrome Associated with Chickenpox

E.S. Hurwitz and R.A. Goodman. Pediatrics 1982 Dec; 70(6):901-6.

Authors' abstract: In the spring of 1980, four confirmed, and three possible cases of Reye syndrome, each associated with a chickenpox prodromal illness, were identified in Las Cruces, New Mexico. One patient, a 5-year-old girl, died. Cases tended to occur in one section of the community, among children attending two of the 16 elementary schools. A telephone survey of parents with school-aged children (6 to 9 years old) suggested that a significantly greater attack rate of chickenpox occurred in children attending those two schools. Based upon this survey and the expected distribution of chickenpox among children less than 15 years of age, the incidence of Reye syndrome following chickenpox infection in the county in which Las Cruces is located was estimated to be 2.5/10,000 cases of chickenpox; these data reveal a four- to ninefold greater incidence of Reye syndrome than that following influenza B infections, which was previously estimated based upon a cluster of five cases in a county in Michigan. Additional investigations of Reye syndrome clusters are needed in an effort to identify and study suspected risk factors and to better define the relationship between Reye syndrome and viral infections.

IgM to Varicella-Zoster Virus: Demonstration in Patients With and Without Clinical Zoster

A.A. Gershon, S.P. Steinberg, W. Borkowsky, D. Lennette and E. Lennette. Pediatr Infect Dis 1982 May-Jun;1(3):164-7.

Authors' abstract: Antibody to varicella-zoster (VZ) virus of the IgM type was detected in sera from 50% of persons with clinical zoster, 67% of asymptomatic varicella immunes with a recent intimate exposure to VZ virus and 22 to 40% of varicella immunes with no symptoms of zoster or known exposure to the virus. No VZ IgM was found in newborn sera or in sera from persons susceptible to varicella, demonstrating specificity of the varicella (VA) IgM assay. Since development of specific IgM is associated with acute infection, these data suggest that reinfection with VA virus occurs and also that antigenic stimulation due to exposure to endogenous VZ virus may occur. We hypothesize that during reactivation of VZ virus, persons with intact VZ cell-mediated immunity (CMI) remain asymptomatic but that those with depressed VZ CMI may develop clinical zoster. These data suggest that there is an unstable relationship between VZ virus and the human host.

Antibody Response to Varicella-Zoster Virus After Natural or Vaccine-Induced Infection

S. Bogger-Goren, K. Baba, P. Hurley, H. Yabuuchi, M. Takahashi and P.L. Ogra. J Infect Dis 1982 Aug;146(2):260-5.

Authors' abstract: The development of serum and nasopharyngeal antibody responses to varicella-zoster virus (VZV) was studied in groups of children after naturally acquired varicella or after immunization with the Oka strain of live attenuated VZV vaccine administered in varying doses via respiratory inhalation or subcutaneous injection. Natural infection, subcutaneous immunization, and respiratory inhalation of large doses of VZV vaccine consistently resulted in the development of VZV-specific IgG antibody responses in serum. Although the serum IgG antibody responses persisted for at least eight to 12 months (to date) after either form of infection, the antibody activity appeared to be four- to eight-fold higher after natural infection than after immunization. Transient IgG antibody responses were observed in serum after respiratory inhalation of smaller doses of VZV vaccine. Natural infection, but not VZV vaccine, was associated with the development of serum and nasopharyngeal IgA responses to VZV in most subjects.

Varicella Zoster in Hospital Personnel: Skin Test Reactivity to Monitor Susceptibility

R.W. Steele, M.A. Coleman, M. Fiser and R.W. Bradsher. Pediatrics 1982 Oct;70(4):604-8.

Authors' abstract: An outbreak of chickenpox, involving three patients and one nurse on a pediatric ward, necessitated rapid identification of susceptible employees in conjunction with standard epidemiologic intervention in order to prevent spread to other high-risk patients. Of 46 hospital personnel 15 (33%) gave a negative or unknown history of prior disease. Response to a varicella-zoster skin test was compared with antibody determination as measured by fluorescent antibody to membrane antigen. Correlation of these two screening methods was absolute. Of 46 hospital personnel, four (9%) were susceptible to infection (negative skin test and antibody less than 1:4) requiring their removal from the ward. All those with positive histories for prior disease with the virus and 11/15 (73%) with negative or unknown histories were immune as indicated by both tests. A readily available varicella zoster skin test would be an extremely useful epidemiologic tool for screening hospital personnel.

An Outbreak of Airborne Nosocomial Varicella

T.L. Gustafson, G.B. Lavely, E.R. Brawner, Jr., R.H. Hutcheson, Jr., P.F. Wright and W. Schaffner. Pediatrics 1982 Oct;70(4):550-6.

Authors' abstract: An outbreak of nosocomial varicella was traced to airborne spread from an immunocompromised child hospitalized from November 11-19, 1980. Seventy potentially susceptible children were hospitalized on the ward during that period. Although the index patient remained in strict room isolation throughout his hospital stay, eight of these patients contracted varicella. The afternoon of November 12 was the period of highest risk for acquiring varicella. Eight of 36 patients (22%) present that afternoon, compared to none of 34 patients not present that afternoon, acquired the infection. A patient's risk of contracting varicella was significantly related to how near he/she came to the index patient's room that afternoon. Airflow studies, using the tracer gas, sulfur hexafluoride (SF6), demonstrated that patient rooms on this ward were at positive pressure with respect to the corridor. Despite isolation procedures, SF6 released in the index patient's room achieved concentrations in the corridor as high as 10% of those inside the room. Airborne spread of varicella has rarely been reported, but it may be a common mode of transmission in hospitals. We suggest that patients hospitalized with varicella be placed in strict isolation in negative-pressure rooms to reduce the risk of nosocomial transmission.

Hospital Infection Control for Varicella Zoster Virus Infection

M.G. Myers, D.A. Rasley and W.J. Hierholzer. Pediatrics 1982 Aug;70(2):199-202.

Authors' abstract: More than 500 hospital employees and 209 patients were exposed to varicella zoster virus (VZV) as a consequence of 22 uncontrolled hospital introductions that occurred over a period of 34 months. Five introductions of varicella were by hospital employees who acquired the infection outside the hospital. Successful infection control of VZV requires an accurate definition of the susceptible population and the limitation of transmission. Individuals with prior VZV infection are epidemiologically not at risk for developing clinical illness. Serologic screening of hospital employees with uncertain prior VZV history is effective in identifying those at risk of developing the infection. A prior history of intimate exposure to VZV does not imply immunity in the absence of clinical illness.

Live Attenuated Varicella Vaccine: Immunization of Healthy Children with the OKA Strain

A.M. Arbeter, S.E. Starr, R.E. Weibel and S.A. Plotkin. J Pediatr 1982 Jun;100(6):886-93.

Authors' abstract: Ninety-one healthy children were immunized with one of three preparations of the OKA strain of live attenuated varicella zoster virus in order to gain sufficient information on safety and immunogenicity to justify vaccine studies in immunosuppressed children. The OKA-Biken vaccine was studied in a dose response trial. Two additional clinical trials were conducted with the OKA strain that was further passaged: a frozen aqueous (OKA-RIT-Aq) form and a lyophilized (OKA-RIT-Ly) form were tested. With each of these vaccines clinical reactivity was minimal and virus shedding, viremia, and transmission of the vaccine virus were absent. Excellent seroconversion rates of 100 and 94% were induced with approximately 500 pfu of OKA-Biken and OKA-RIT-Ly vaccine, respectively. A lower seroconversion rate was noted for OKA-RIT-Aq, presumably on the basis of defective individual vials. Diluted OKA-Biken vaccine induced less seroconversion but even the 5 pfu dose produced antibody responses in 81% of the vaccinees. In vitro specific cellular immune responses to varicella virus antigens were demonstrated in each group of vaccinees, including all but two of those vaccinees who failed to seroconvert. The data indicate that two preparations of the OKA strain are sufficiently safe and immunogenic in healthy children to support further studies in immunocompromised children.

Live Attenuated Varicella Vaccine: The KMcC Strain in Healthy Children

A.M. Arbeter, S.E. Starr, R.E. Weibel, B.J. Neff and S.A. Plotkin. Pediatrics 1983 Mar;71(3):307-12.

Authors' abstract: The KMcC strain of live, attenuated varicella-zoster virus vaccine was studied in healthy children as a preliminary step toward varicella vaccine studies with this strain in children with leukemia. Forty-three children were immunized: 26 with the 40th passage vaccine and 17 with the 50th passage. Studies included surveillance for clinical reactivity, oropharyngeal excretion of vaccine virus, viruria, and viremia. Antibody responses were assayed by fluorescent antibody to membrane antigens and immune adherence hemagglutination. Cell-mediated immune responses were assayed by lymphocyte proliferation to varicella-zoster virus specific antigens. There was 100% seroconversion to the KMcC passage 40 and 50 vaccines (by fluorescent antibody to membrane antigen assay). Every child studied developed in vitro lymphocyte proliferation to varicella-zoster virus antigens. Papular skin lesions, probably vaccine related, occurred in 31% of the 40th passage vaccinees but in only 6% of the 50th passage vaccinees. The 50th passage KMcC strain vaccine is sufficiently immunogenic and safe to initiate clinical studies with leukemia patients.

Protective Effect of Immediate Inoculation of a Live Varicella Vaccine in Household Contacts in Relation to the Viral Dose and Interval Between Exposure and Vaccination

Y. Asano, S. Hirose, S. Iwayama, T. Miyata, T. Yazaki, and M. Takahashi. Biken J 1982 Mar;25(1):43-5.

Authors' abstract: The protective effect on 45 household contacts of immediate inoculation of a live varicella vaccine was examined in relation to the viral dose and days after exposure to varicella. The viral doses used were 300 PFU to 15,000 PFU, and the intervals between exposure and vaccination were 0 to 5 days. All 30 contacts given viral doses of 800 to 15,000 PFU within 3 days after exposure were protected from clinical varicella. With lower viral doses of 300 to 600 PFU within 3 days after exposure, 6 to 10 contacts developed rashes 13 to 25 days after vaccination, but all showed mild symptoms. When vaccine was given 5 days after exposure, even with a dose of 1,500 to 4,000 PFU, typical varicella symptoms appeared 6 to 9 days after vaccination. These results suggest that vaccination of household contacts with viral doses of over 500-800 PFU within 3 days after exposure is effective in preventing manifestation of clinical varicella and that clinical symptoms may be modified to a mild form by vaccination with even a lower viral dose when given within 3 days after exposure.

Application of a Live Varicella Vaccine to Hospitalized Children and Its Follow-up Study

N. Katsushima, N. Yazaki, M. Sakamoto, J. Fujiyama, M. Nakagawa and Y. Okuyama. Biken J 1982;25:29-42.

Authors' summary: One hundred and 50 patients, including 35 immunocompromised patients were given a live varicella vaccine. The occasions for vaccinations were 11 times for protection of successive nosocomial infection on occurrence of cases of varicella in a pediatric ward (97 subjects), once for the same purpose in a nursery (13 subjects) and non-urgent vaccination for 7 immunocompromised patients, 32 healthy susceptible children and 1 nurse. Viral doses used were 250 to 5,000 PFU. Without exception successive outbreaks of varicella in the ward and nursery were prevented when the vaccine was used 1 to 5 days after the onset of varicella. Humoral and/or cellular immunity was acquired in 97.1% of the high risk group and 91.9% of the non-high risk group. As for the clinical reactions, rashes and fever were seen in 47.1% and 17.6%, respectively, of the high risk group and 8.0% and 0.9% of the non-high risk group. The symptoms were generally mild.

A follow-up study on the vaccinated subjects from 6 months to 3 years and 10 months after vaccination showed that in the high risk group 23 of 25 cases had sustained antibody determined by immunoadherence hemagglutination (IAHA) or fluorescent antibody to membrane antigen (FAMA) test and 23 of 25 cases gave a positive skin reaction, and 24 of 24 cases had sustained antibody and 20 of 21 cases gave a positive skin reaction in the non-high risk group. Of 32 patients in the high risk group, 2 showed herpes zoster and 4 developed clinical varicella and 4 developed clinical varicella after 13 occasions of contact with varicella patients. Both varicella and zoster symptoms in the vaccinees were mild except in 1 case with leukemia in relapse, who showed moderate symptoms.

In a retrospective study, 11 of 31 unvaccinated high risk patients in our hospital caught natural varicella during treatment or remission and in 6 of them the disease was moderate or severe. Herpes zoster occurred in 3 of 31 cases and was severe in 2. Thus the benefit of varicella vaccination is unquestionable; it prevented successive outbreaks in the ward and protected high risk patients from severe or fatal varicella. However, revaccination is advisable if immunity against varicella declines to an undetectable level in high risk children who are receiving immunosuppressive therapy.

Administration of Live Varicella Vaccine to Children with Leukemia

P.A. Brunell, Z. Shehab, C. Geiser and J.E. Waugh. Lancet 1982 Nov 13;2(8307):1069-73.

Authors' abstract: Live varicella vaccine was given to twenty-three children with lymphoreticular malignancies, twelve whose chemotherapy was complete and eleven who were still receiving therapy. Seroconversion was observed in all twenty-three children, only one of whom lost his vaccine-induced antibody. Eight of the children experienced thirteen exposures to varicella, including four continuing exposures in their households. Varicella, manifested by the appearance of seven vesicular lesions, developed in only one. In all but two of the children an in vitro blastogenic response to varicella/zoster-virus (VZV) antigen developed; both children had a biphasic rash after immunization. A sibling of one of these children seroconverted without clinical evidence of varicella, presumably because of infection with vaccine virus. None of the other household contacts had significant rises in VZV antibody. VZV was not isolated from the blood, throat, or urine samples of the twenty-three vaccinees tested.

Viral Hepatitis

Progress Toward a Live, Attenuated Human Hepatitis A Vaccine

P.J. Provost, F.S. Banker, P.A. Giesa, W.J. McAleer and E.B. Buynak. Proc Soc Exp Biol Med 1982 May;170(1):8-14.

Authors' abstract: Human hepatitis A virus was attenuated in virulence for marmosets by passage in FRhK6 and human diploid lung fibroblast cell cultures. A number of variants were produced that showed different levels of virulence/attenuation for marmosets. Marmosets that had attenuated virus-like responses following injection of variant virus were challenged with virulent virus; all were solidly immune to infection. Antibody stimulated by the vaccine equated with protection. These findings show that human hepatitis A virus can be attenuated and show the feasbility for eventual development of a live, attenuated hepatitis A vaccine for human use.

Postnatal Infectivity of Hepatitis B Surface Antigen-Carrier Mothers

R.P. Beasley and L.Y. Hwang. J Infect Dis 1983 Feb;147(2):185-90.

Authors' abstract: The incidence of hepatitis B virus (HBV) infections during the second and third year of life was determined for 105 children whose mothers were carriers of hepatitis B surface antigen. Children were given hepatitis B immune globulin (HBIG) at birth and in some instances three and six months later to protect against HBV infection. Passive antibodies from the dose of HBIG disappeared in three to four months. Infants negative for HBV markers at 12 months were selected and subsequent infections were analyzed in relation to the e system markers in the mother. Over an average of 17.5 months of follow-up, 38.1% of the infants became infected, an annual incidence rate of 26.0%. The rate was highest for children whose mothers were positive for hepatitis B e antigen (HBeAg) (57.1%), moderate for those whose mothers were negative for both HBeAg and antibody to HBeAg (anti-HBe) (20.4%), and lowest for those whose mothers were positive for anti-HBe (11.3%).

The Newly Licensed Hepatitis B Vaccine. Characteristics and Indications for Use

S. Krugman. JAMA 1982 Apr 9;247(14):2012-5.

Author's abstract: The inactivated hepatitis B vaccine that was licensed in November 1981 will be distributed for general use later this year. Extensive studies have confirmed the safety, immunogenicity, and remarkable efficacy of this vaccine for the prevention of acute hepatitis B disease, asymptomatic infection, and the chronic hepatitis B carrier state. The vaccine is recommended for immunization of infants, children, and adults who are considered to be at increased risk of contracting hepatitis B infection. These population groups include medical, dental, laboratory, and other health care personnel, selected patients (e.g., hemodialysis, thalassemia), clients and staff of institutions for the mentally disabled, homosexually active males, intimate contacts of carriers, users of illicit drugs, infants in high-risk areas, and other high-risk groups. The availability and appropriate use of the newly licensed hepatitis B vaccine should enable physicians to prevent a serious cause of acute and chronic liver disease.

The Prevention of Hepatitis B with Vaccine. Report of the Centers for Disease Control Multi-Center Efficacy Trial Among Homosexual Men

D.P. Francis, S.C. Hadler, S.E. Thompson, J.E. Maynard, D.G. Ostrow, N. Altman, E.H. Braff, P. O'Malley, D. Hawkins, F.N. Judson, K. Penley, T. Nylund, G. Christie, F. Meyers, J.N. Moore, Jr., A. Gardner, I.L. Doto, J.H. Miller, G.H. Reynolds, B.L. Murphy, C.A. Schable, B.T. Clark, J.W. Curran and A.G. Redeker. Ann Intern Med 1982 Sep;97(3):362-6.

Authors abstract: A randomized, double-blind, vaccine/placebo trial of the Merck 20-micrograms hepatitis B virus (HBV) vaccine was done among 1402 homosexual men attending venereal disease clinics in five American cities. Vaccination was followed by only minimal side effects. Two doses of vaccine induced antibody in 80% of vaccine recipients. A booster dose 6 months after the first dose induced antibody in 85% of recipients and markedly increased the proportion of recipients who produced high antibody titers. The incidence of HBV events was markedly less in the vaccine recipients compared to that in the placebo recipients ($p=0.0004$). Between month 3 and 15 after the first dose, 56 more significant HBV events (hepatitis, or hepatitis B surface antigen positive, or both) occurred in the placebo group while only 11 occurred in the vaccine group. Ten of the 11 HBV events in the vaccine recipients occurred in hypo- or non-responders to the vaccine. This vaccine appears to be safe, immunogenic, and efficacious in preventing infection with hepatitis B virus.

Hepatitis B Virus Vaccine Safety: Report of an Inter-Agency Group

Anonymous. MMWR 1982 Sep 3;31(34):465-7.

In response to requests for additional information on the safety of the inactivated hepatitis B virus (HBV) vaccine recently recommended for use by the Immunization Practices Advisory Committee (ACIP), the Inter-Agency Group to Monitor Vaccine Development, Production, and Usage, with representatives from the Centers for Disease Control, Food and Drug Administration, and National Institutes of Health, has further reviewed the available data. Its conclusions on vaccine production and safety evaluation support the ACIP statement on hepatitis vaccine and can be summarized as follows: 1) immediate side effects are minimal after receipt of HBV vaccine; 2) no long-term reactions have been reported; 3) the purification and inactivation process is known to inactivate representatives of all known groups of animal viruses; 4) each lot is safety tested in primates; 5) no known causes of hepatitis B or non-A/non-B hepatitis have been transmitted by the vaccine and no known occurrence of AIDS has been associated with the vaccine.

Indications For Use of Hepatitis B Vaccine, Based on Cost-Effectiveness Analysis

A.G. Mulley, M.D. Silverstein and J.L. Dienstag. N Engl J Med 1982 Sep 9;307(11):644-52.

Authors' abstract: To formulate indications for the use of hepatitis B vaccine, we examined the cost effectiveness of three strategies: vaccinating everyone; screening everyone and vaccinating those without evidence of immunity; and neither vaccinating nor screening, but passively immunizing those with known exposure. Estimates of the hepatitis attack rate, prevalence of immunity, and frequency of known exposure were made for three representative populations: homosexual men, surgical residents, and the general population of the United States. Screening followed by vaccination of homosexual

men and vaccination without prior screening of surgical residents would result in savings of medical costs. Neither screening nor vaccination is the lowest-cost strategy for the general population. Vaccination of susceptible persons will save medical costs for populations with annual attack rates above 5 percent. Vaccination may be considered cost effective (or cost saving when indirect costs are included) for populations with attack rates as low as 1 to 2 percent.

Comparison of Safety and Immunogenicity of ADW and AYW Hepatitis B Vaccines

G.J. Papaevangelou, C.G. Vissoulis, A.J. Roumeliotou-Karayannis, N. Kolaitis and S. Krugman. J Med Virol 1982;9(3):231-6.

Authors' abstract: The safety and immunogenicity of adw and ayw hepatitis B vaccines were compared in a double-blind randomized trial in Greek Air Force recruits. One hundred and ten out of 240 eligible nonimmune recruits were randomly selected and allocated to the two vaccine treatment groups. Two 20-micrograms doses 1 month apart and a third 20-micrograms booster dose, at 6 months, were given intramuscularly. Severe local or general side effects were not observed. The frequency of mild side effects (local discomfort or pain, fever less than 37.5° C, and malaise) was slightly higher with the ayw vaccine than with the adw. Antibodies developed earlier and in higher titers in adw vaccinees. However, after the booster dose all ayw and all but one adw vaccinees developed anti-HBs in almost similar titers. It is concluded that both vaccines are equally safe and immunogenic after administration of two doses at a 1-month interval followed by a booster dose at 6 months.

Immune Response in Neonates to Hepatitis B Vaccine

F. Barin, A. Goudeau, F. Denis, B. Yvonnet, J.P. Chiron, P. Coursaget and I.D. Mar. Lancet 1982 Jan 30;1(8266):251-3.

Authors' abstract: Three injections of alum hepatitis B vaccine (HB vaccine) were given to 26 Senegalese infants, the first when they were less than 1 month old, and the second and third after 1-month intervals. Ninety-five percent of the neonates whose serum was negative for hepatitis B surface antigen and antibodies against the surface antigen (anti-HBs) showed a specific anti-HBs response. Anti-HBs titers in the neonates were similar to those previously obtained in Senegalese children aged 1-24 months. HB vaccine was without side-effects and was immunogenic in the neonates, irrespective of the hepatitis-B-marker status of the mothers or the children.

Hepatitis B Vaccine Administered to Chronic Carriers of Hepatitis B Surface Antigen

J.L. Dienstag, C.E. Stevens, A.K. Bhan and W. Szmuness. Ann Intern Med 1982 May;96(5):575-9.

Authors' abstract: We administered up to 6 monthly doses of hepatitis B vaccine to 16 chronic carriers of hepatitis B surface antigen (HBsAg) in an attempt to eliminate the antigen. The HBsAg in this vaccine differs from native antigen. No patients had elimination of HBsAg, but one of 10 no longer carried hepatitis B e antigen (HBeAg). Of 13 patients without preexisting antibody to HBsAg (anti-HBs), none acquired the antibody; two of three patients with preexisting heterotypic anti-HBs had transient, low-level increases in anti-HBs titers. Serum alanine aminotransaminase (ALT) levels fell in eight patients, remained unchanged in six, and increased transiently in two. Decreased ALT and HBeAg clearance, however, did not seem to be related to vaccination, and the transient ALT elevations appeared to represent sporadic, acute non-A, non-B hepatitis. No adverse effects other than sore arm and joint pain were seen. Immunization of chronic HBsAg carriers with hepatitis B vaccine, although ineffective in eliminating HBsAg, appeared to be safe. Such safety, if confirmed, would simplify the design of hepatitis B vaccination programs.

Combined Passive and Active Immunization for Preventing Perinatal Transmission of Hepatitis B Virus Carrier State

H. Tada, M. Yanagida, J. Mishina, T. Fujii, K. Baba, S. Ishikawa, S. Aihara, F. Tsuda, Y. Miyakawa and M. Mayumi. Pediatrics 1982 Oct;70(4):613-9.

Authors' abstract: Prevention of perinatal transmission of hepatitis B virus carrier state in neonates at high risk was attempted by a combined passive and active immunization. Immediately after delivery, ten babies born to mothers who were asymptomatic carriers of hepatitis B surface antigen (HBsAg) and seropositive for hepatitis B e antigen received an intravenous injection of F(ab')2 fragments (200 IU) derived from hepatitis B immune globulin (HBIG). On the following day, none of them revealed detectable levels of the antibody to HBsAg in their sera, and received an intramuscular injection of HBIG (200 IU) which was repeated at 2 and 4 months of age. Vaccination with 40 micrograms of purified, formalin-inactivated HBsAg particles was given to the nine babies at three months and repeated at 4, 5, and 7 months after birth. All of them maintained detectable levels of the antibody and escaped infection throughout the first 12 months of their lives. The one baby who did not have detectable F(ab')2 in serum for 24 hours developed persistent HBs antigenemia which was noticed as early as seven days after birth.

Hepatitis B Immunity in Hospital Staff Targeted for Vaccination. Role of Screening Tests in Immunization Programs

G.F. Grady. JAMA 1982 Nov 12;248(18):2266-9.

Author's abstract: To estimate how many hospital workers might be exempted from immunization with newly available but expensive hepatitis B vaccine, baseline serum samples were analyzed to determine prevalence and titer of hepatitis B (HB) surface antibody (anti-HBs) and prevalence of core antibody (anti-HBc). Among 1,370 persons tested, anti-HBs was present in 279 (20.4%), including 192 (14.0%) with titers of 10 ratio units or greater. In a subset of 746 subjects who denied recent exposures, and who were tested for anti-HBc and anti-HBs, at least one of the two antibodies was found in 172 (23.1%). There were 47 (6.3%) who had anti-HBs alone and 27 (3.6%) with anti-HBc alone. Prevalence was related more closely to clinical service (e.g., renal dialysis or surgery) than to title (e.g., physician or technician).

Hepatitis B in Hemodialysis: Vaccination Against HBs Antigen

J. Crosnier. Proc Eur Dial Transplant Assoc 1981;18: 231-40.

Author's abstract: Institut Pasteur Production vaccine, prepared from plasma of chronic carriers of HBsAg (ad + ay sub-types) negative for HBeAg, inactivated by formaldehyde, containing 5 micrograms HBsAg per 1ml dose, with Al $(OH)_3$ as adjuvant, was tested in a multicenter efficacy trial. After informed consent and exclusion of subjects positive for HBsAg, anti-HBc or anti-HBs, 367 permanent staff members and 138 chronic hemodialysis patients from 64 centers were enrolled in the trial. They received randomly, double-blind, 3 subcutaneous doses of either vaccine (V) or placebo (P) at one-month intervals and were followed monthly for one year. The incidence of HBV infections was significantly lower in V than in P recipients, in staff and in patients. In staff members, no HBV infections occurred in V recipients after the second injection, whereas they were distributed throughout the whole 12 month follow-up period in P recipients. Anti-HBs titers $\geq$10mIU/ml were obtained in 94% of vaccinated subjects. Antibody peak (mean ± 2 SE) reached 2433 ± 1077mIU/ml two months after the third injection, with a further rise to about 30 times this value following a booster injection, 16 ± 2 months after the first injection. These results demonstrate the immunogenicity and efficacy of Institut Pasteur Production hepatitis B vaccine.

Vaccination Against Hepatitis B in a Hemodialysis Unit. A 4-Year Follow-Up (French)

J. Pengloan, P. Bagros, J.L. Jourdan, H. Nivet, A. Goudeau, F. Dubois and F. Barin. Nephrologie 1982;3(1):32-5.

English summary: From February 1976 to January 1980, 123 staff members and 84 hemodialysis patients were immunized against hepatitis B in an adult hemodialysis unit. The vaccine was prepared by purification of HBs Ag from human sera and was formalin inactivated. Vaccines were tested for serologic markers of HB virus (HBs Ag, anti-HBs, anti-HBc) and serum transaminases (ALT, AST) before immunization and every month during the follow-up. Tests for markers of auto-immunity were performed. The vaccinees were followed from 4 to 48 months. No evidence of long-lasting reactions to the HB vaccine or auto-immunity was observed. Ninety-one percent of the staff members seroconverted for anti-HBs; none of them showed clinical, biologic or serologic signs of active HB infection; 62% of the hemodialysis patients sero-converted for anti-HBs; none of them became HBs Ag chronic carriers. These results were obtained despite the fact that the prevalence of HBs Ag chronic carriers was 32.7% when the study began. Active immunization proved to be a safer and efficient method of preventing HB infection in a hemodialysis unit.

Vaccine Against Hepatitis B in Children: Prevention of Hepatitis in a Pediatric Hemodialysis Unit

H. Nivet, J. Drucker, F. Dubois, A. Goudeau, P. Coursaget, J.C. Rolland, B. Grenier and P. Maupas. Int J Pediatr Nephrol 1982 Mar;3(1):25-8.

Authors' abstract: In a pediatric hemodialysis unit, 10 children (aged 1 to 14 years) with chronic renal failure were immunized against hepatitis B infection (HB) by means of a vaccine. The vaccine was prepared by purification of hepatitis B surface antigen (HBs Ag) from human sera and was formalin inactivated. Seven children were undergoing periodic hemodialysis and three were still managed with conservative treatment. Three HBs Ag chronic carriers children were also dialysed in the unit and therefore represented a permanent high risk of HB for the whole unit. All the vaccinated children sero-converted for antibody to HBs Ag (anti-HBs) after vaccination. A follow-up from 16 to 33 months did not reveal clinical, biological or serological signs of hepatitis B in the vaccinated children. Presence of anti-HBs and absence of appearance of hepatitis B following immunization suggest that hepatitis B vaccine has represented for these children an effective means of prevention against hepatitis B infection.

Hepatitis B Vaccine in Medical Staff of Hemodialysis Units: Efficacy and Subtype Cross-Protection

W. Szmuness, C.E. Stevens, E.J. Harley, E.A. Zang, H.J. Alter, P.E. Taylor, A. DeVera, G.T. Chen and A. Kellner. N Engl J Med 1982 Dec 9;307(24):1481-6.

Authors' abstract: We evaluated the efficacy of hepatitis B vaccine (Heptavax-B) containing only the ad subtype in a randomized, placebo-controlled, double-blind trial among 865 staff members of 43 hemodialysis units in the United States. Surface antibody developed in 92.6 percent of the subjects after two doses of vaccine and in 96 percent after the six-month booster. The incidence of infections with hepatitis B virus (with or without hepatitis) was 9.9 percent in placebo recipients and 2.2 percent in vaccine recipients ($p < 0.01$). The two cases of hepatitis B among vaccine recipients did not occur in subjects in whom antibody had developed. In 81 percent of the hepatitis events, the virus was of the ay subtype. The incidence of ay virus was 8.2 percent among placebo recipients and 1.2 percent among vaccine recipients ($p < 0.005$). We conclude that these data confirm the efficacy of the vaccine and demonstrate subtype cross-protection.

Induction of Cell-Mediated Immunity to HBsAg Polypeptides

T. Kremastinou, C.R. Howard, J. Skelly and A.J. Zuckerman. Intervirology 1981;16(3):176-83.

Authors' abstract: Adult male guinea pigs were immunized with hepatitis B virus polypeptides prepared by Triton X-100 solubilization of purified 22-nm hepatitis B surface antigen (HBsAg) particles. A virus-specific subunit containing both the 28,000 molecular weight glycoprotein and the 23,000 molecular weight protein stimulated both cell-mediated and humoral immunity. A whole-blood-cell transformation assay additionally showed that the 64,000 molecular weight component of HBsAg, previously shown to contain host-specific antigens, also stimulated a cellular response to purified intact HBsAg particles, suggesting the additional presence of virus-specific material in this fraction. Immunization of animals with the 28,000—23,000 molecular weight polypeptides subsequently prepared in micelle form enhanced the demonstration of a cell-mediated reaction after only a single dose of immunogen. The results provide further evidence as to the suitability of HBsAg polypeptides prepared by Triton X-100 solubilization for hepatitis B prophylaxis.

Uptake and Elimination of Hepatitis B Immunoglobulin after Intramuscular Administration (German)

N. Scheiermann and E.K. Kuwert. Dtsch Med Wochenschr 1982 Dec 17;107(50):1918-22.

English summary: After intramuscular administration of four different hepatitis B immunoglobulins at a dose of 0.1 ml/kg body weight, serum anti-HBs antibody titers were followed over four months in 37 healthy persons. Highest serum concentration averaged 138-355 mU anti-HBs/ml and was generally observed on the third or seventh day after passive immunization. Immunoglobulins were eliminated with a half-life of 17.5—25 days. Four months after injection their concentration was still 1.2—2.5% of the maximally reached serum level. Intramuscular administration of hepatitis B immunoglobulin does not at once achieve effective optimal viral antibody levels in blood. But since there are no special preparations for intravenous use and active immunization is unlikely to be able to provide immediate protection against hepatitis B virus, intramuscular injection continues to remain the method of choice in the prevention of hepatitis B after exposure.

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VACCINES, TOXOIDS, AND ANTIVIRAL AGENTS

GENERAL

Vaccines and Toxoids

New Opportunities for Development of Safe, Effective Live Virus Vaccines

R.M. Chanock. Yale J Biol Med 1982 May-Aug;55 (3-4):361-7.

Author's abstract: Effective vaccines are not available for most viral diseases. This situation may soon change when the full force of contemporary molecular biology is applied to immunoprophylaxis. In certain viral diseases, particularly those affecting the respiratory and gastrointestinal tracts, live attenuated vaccines are needed to confer effective protection. Until now the major obstacle to success has been genetic instability. It may be possible to construct stable, satisfactorily attenuated mutants by cloning viral DNA or RNA and then subjecting the cloned DNA to enzyme surgery to create viable deletion mutations. Modified cloned DNA derived from positive-strand viral RNA could then be transferred back into its virus by transfection of cells. Conversion of mutant cloned DNA into negative-strand RNA and transfer into its virus will require a more elaborate type of rescue.

Neurological Complications of Immunization

G.M. Fenichel. Ann Neurol 1982 Aug;12(2):119-28.

Author's abstract: Vaccines prepared from whole, killed organisms (pertussis and possibly influenza) may cause neurological allergic reactions producing encephalopathy. These reactions are characterized by acute, monophasic demyelinative processes and occur with no greater frequency than 1 per 100,000 vaccine recipients; onset is within 4 days of immunization, and recovery is usually complete. No evidence suggests that these vaccines produce an insidious, progressive encephalopathy. Only with the swine influenza program of 1976 has Guillain-Barré syndrome appeared to follow immunization. Vaccines prepared from live-attenuated viruses (measles, mumps, rubella, and trivalent oral poliovirus) can cause symptomatic viral infection of the nervous system, including measles encephalitis, which occurs in 1 of 1,000,000 vaccine recipients; rubella neuritis, in less than 1 of 10,000 recipients; and paralytic poliomyelitis, in 1 of 3,000,000 vaccine recipients or their close contacts. A cause-and-effect relationship between immunization and brachial plexus neuritis, acute transverse myelitis, and cranial neuropathies has been suggested but never proved.

Antiviral Agents

Comparative Toxicity of Amantadine Hydrochloride and Rimantadine Hydrochloride in Healthy Adults

F.G. Hayden, J.M. Gwaltney, Jr., R.L. Van de Castle, K.F. Adams and B. Giordani. Antimicrob Agents Chemother 1981 Feb;19(2):226-33.

Authors' abstract: The relative toxicities of amantadine and rimantadine were compared in a double-blind, placebo-controlled study involving healthy adults. In separate studies, drugs were administered at a dosage of 200 mg/day (52 volunteers) or 300 mg/day (196 volunteers) for 4.5 days. Both drugs were well tolerated at the lower dosage. At 300 mg/day amantadine recipients had a greater frequency and severity of central nervous system (nervousness, lightheadedness, difficulty concentrating) and sleep (insomnia, fatigue) complaints compared with rimantadine or placebo recipients. Amantadine recipients also performed less well on an objective test measuring sustained attention and problem-solving ability. Both amantadine and rimantadine recipients reported adverse gastrointestinal symptoms more often than placebo recipients. Because of better tolerance at higher dosage, rimantadine offers more promise than amantadine for treatment of influenza A virus infections.

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IMMUNIZATION—GENERAL

General

Benefits, Risks and Costs of Viral Vaccines

J.P. Koplan and N.W. Axnick. Prog Med Virol 1982;28: 180-91.

Authors' abstract: The techniques of benefit-risk, benefit-cost and cost-effectiveness analysis have been applied to several vaccines. The analyses are useful to the scientific community, and to public health practitioners and administrators. The studies can also put vaccination programs in an economic perspective for policy makers, legislators, other budget allocators and planners. They permit investigators to focus on crucial variables in decision-making which are in need of better biologic or epidemiologic information and thus help direct research. They promote the use of valuable vaccines in places not currently engaged in vaccination programs (e.g., measles) and discourage the misuse of inappropriate vaccines (e.g., smallpox). It is worth noting that the studies we have reviewed are aimed at public health, not at individual clinical decision-making. Benefits, risks and costs have been viewed from a societal perspective. For decisions on the use of viral vaccines for particular individuals, different conclusions might be reached. Thus, killed poliomyelitis vaccine might be preferable for some persons. Boys receive rubella vaccine less for their immediate benefit than for the benefit of society as a whole and the role these young male recipients play in disease transmission to potentially infected pregnant contacts.

The variables that make a given vaccine cost-beneficial vary with each vaccine. The long-term disabilities of paralytic poliomyelitis and the complications of measles constitute major cost factors for these diseases. Most of the costs of mumps arise from the acute illness. The immediate complicatons of the acute illness are major cost factors in influenza. For rubella, the considerable disabilities of fetal infection provide the major costs.

Benefit-risk, benefit-cost and cost-effectiveness analyses can be useful in determining target groups or strategies for vaccination programs. The newly developed hepatitis B vaccine might be most economically distributed with the largest public health impact if a benefit-cost analysis were done to determine which target populations should receive it.

Cost-Effectiveness Appraisal of Immunization Programs

A.L. Creese, N. Sriyabbaya, G. Casabal and G. Wiseso. Bull WHO 1982;60(4):621-32.

Authors' abstract: This paper describes a cost-effectiveness analysis of the immunization programs of Indonesia, the Philippines, and Thailand, using the program costing guidelines developed for the WHO Expanded Program on Immunization (EPI). The principal organizational features of each program are outlined, and total costs and costs per fully immunized infant are assessed at a small sample of health centers in each country. Costs were found to average US$2.86 in Indonesia, US$4.97 in the Phillipines, and US$10.73 in Thailand. At each health center the main element of total immunization costs was fixed, so that average costs per fully immunized chiid fell as coverage levels and activity rates rose. The implications of this preliminary analysis are considered for each country and common managerial issues in EPI in particular, and primary health care in general, are detailed. Program organization, health care input costs, and population accessibility are considered as explanations of the observed differences in immunization cost. The feasibility of undertaking routine cost-effectiveness monitoring of immunization and other primary health care programs is considered.

Vaccination and Disease Prevention in Adults

R.A. Goodman, W.A. Orenstein and A.R. Hinman. JAMA 1982 Oct 1;248(13):1607-10.

From authors' discussion: Because an increased proportion of vaccine-preventable diseases now occur in adults, and because new vaccines are being continually introduced, physicians and other health care workers should increase their familiarity with, and use of, vaccines in adults as well as in children.

A carefully obtained medical history can help to prevent the occurrence of potentially severe vaccine-preventable diseases of children and adults. Information required includes the patient's previous vaccinations and history of vaccine-preventable illnesses and knowledge of which vaccines are indicated. Information concerning the vaccination history can be recorded and should include a review of vaccines that are recommended universally for children in the United States (diphtheria, measles, mumps, pertussis, poliomyelitis, rubella, and tetanus) and of vaccines recommended for persons in all age groups who are at increased risk for certain infections or their complications—for example, influenza vaccine for patients with sickle cell anemia, or hepatitis B vaccination status of household contacts of hepatitis B cases or health care workers. Preferably, vaccine histories should be based on written documents to ensure that vaccines or toxoids were administered at the proper ages and intervals.

For the vaccines and toxoids discussed in this commentary, published recommendations and package inserts should be reviewed for more detail concerning contraindications, adverse reactions, indications, dosage, and mode of administration. If further assistance is needed, authorities of county and state health departments or the Centers for Disease Control (CDC) may be contacted.

Directly Transmitted Infectious Diseases: Control by Vaccination

R.M. Anderson and R.M. May. Science 1982 Feb 26;215(4536):1053-60.

Authors' abstract: Mathematical models for the dynamics of directly transmitted viral and bacterial infections are guides to the understanding of observed patterns in the age-specific incidence of some common childhood diseases of humans, before and after the advent of vaccination programs. For those infections that show recurrent epidemic behavior, the interepidemic period can be related to parameters characterizing the infection (such as latent and infectious periods and the average age of first infection); this relation agrees with the data of a variety of childhood diseases. Criteria for the eradication of a disease are given, in terms of the proportion of the population to be vaccinated and the age-specific vaccination schedule. These criteria are compared with a detailed analysis of the vaccination programs against measles and whooping cough in Britain, and estimates are made of the levels of protection that would be needed to eradicate these diseases.

Vaccinations and the Physically Handicapped Child

R.C. Tervo and B. Taylor. Can Med Assoc J 1982 Sep 15;127(6):475-7.

Authors' abstract: The vaccination status of 98 physically handicapped children was examined to identify factors associated with an inadequate vaccination status. Of the 98 children, 57 had cerebral palsy, 14 had myelomeningocele, 3 had muscular dystrophy and 24 had other motor disabilities. According to the available vaccination records, only 17 children had received all the recommended injections on schedule; 26 had missed at least one injection, and 3 of them had never been vaccinated. The overall rate of vaccination in our study group (63%) was lower than expected. The children with moderate to severe limitation of function due to cerebral palsy were significantly less likely ($p<0.05$) than those with less severe limitations to have received a basic series of vaccinations. Health departments must ensure that physically handicapped children receive the preventive health measures viewed normal and appropriate for other children.

Serological Survey: Immunity to Vaccine Preventable Diseases Among Detainees at a Juvenile Hall Facility

M.A. Strassburg, C.J. Baker, W. Minkowski and L. Friedlander. J Adolesc Health Care 1982 Sep;3(2):91-5.

Authors' abstract: Sera from 378 juveniles interned in a juvenile hall facility between February and March 1978, were tested for antibody to polio viruses types 1, 2, and 3; diphtheria; tetanus; measles; and rubella. Only 57% of juveniles ages 11-18 years had neutralizing antibody ≥1:8 to all three types of polio viruses. Juveniles most often lacked antibody to polio type 3. Over 92% of juveniles tested had a protective level of antitoxin (≥.01 U/ml) to diphtheria and tetanus. Hemagglutination inhibition (HAI) antibody tests performed for measles and rubella revealed 87.5% and 81% with titers ≥1:8, respectively. No major differences in immune status were found between those with a previously documented vaccination history and those without. Based on these data, a uniform immunization policy was adopted for Los Angeles County's Juvenile Hall Facilities.

Cluster Sampling to Assess Immunization Coverage: A Review of Experience With a Simplified Sampling Method

R.H. Henderson and T. Sundaresan. Bull WHO 1982;60(2):253-60.

Authors' abstract: A simplified cluster method, involving the random selection of 210 children in 30 clusters of 7 children each, has been used by the Expanded Programme of Immunization to estimate immunization coverage. This paper analyzes the performance of the method in 60 actual surveys and 1500 computer simulated surveys. Although the method gives a proportion of results with confidence limits exceeding the desired maximum of ± 10 absolute percentage points, it is concluded that it performs satisfactorily.

Immunization and Cot Deaths (Letter)

E.M Taylor and J.L. Emergy. Lancet 1982 Sep 25;2 (8300):721.

From authors' letter: During the first three years (April 1, 1979, to March 31, 1982) of the present stage of confidential inquiries into infant deaths in Sheffield, 26 deaths were certified as "unexpected death in infancy." An immunization history was obtained on all of these infants and confirmed from central immunization records. Two age matched controls were selected for each case (the tenth preceding and succeeding births from each index child in the birth notification register) and a record of immunization (excluding BCG) before the date of death of the index case was obtained for every control child from central immunization records.

The results show that, in Sheffield, babies who die unexpectedly are slightly less likely to have received any form of immunization ($p>0.05$) than control infants and reveal no significant relation between recent immunization and sudden unexpected death. This suggests that in our community, immunization is certainly not a major factor in the general etiology of sudden infant deaths. However, in our experience, most unexpected deaths have a multifactorial etiology and we cannot exclude the possibility of recent immunization being one of several contributory factors in an occasional unexpected infant death.

Seizures Following Childhood Immunizations

D.G. Hirtz, K.B. Nelson and J.H. Ellenberg. J Pediatr 1983 Jan;102(1):14-8.

Authors' abstract: In 1.4% of children who experienced a seizure during the first seven years of life, the seizure followed within two weeks of an immunization procedure. We report 40 postimmunization seizures in 39 children enrolled in the Collaborative Perinatal Project. Ten seizures followed diphtheria-pertussis-tetanus (DPT) immunization, and 10 followed measles immunization. All but one of the seizures were associated with fever, often high. Thirty-seven seizures lasted less than 30 minutes. More than half of the children had a personal or immediate-family history of febrile seizures. One of the children had a right focal seizure lasting six hours after DPT immunization and had a significant speech deficit on long-term follow-up. No child developed epilepsy, and results in all children with brief seizures were normal on neurologic and cognitive examination at 7 years of age. Both in clinical presentation and generally benign outcome, these immunization-related seizures closely resemble febrile seizures, which are common in early childhood.

Health Care Delivery

A Novel Single-Dose Delivery System for Vaccines

W.J. McAleer, H.Z. Markus, E.B. Buynak, R.E. Weibel, V.M. Villarejos, A.A. McLean, and M.R. Hilleman. J Biol Stand 1982 Oct;10(4):329-33.

Authors' abstract: A single-dose, low-cost vaccine delivery system (Ezeject) consisting of lyophilized measles (Moraten-Attenuvax) vaccine loaded into a pre-filled single-dose plastic syringe with a squeezable body portion has been developed in these laboratories. Data concerning the preparation and properties of vaccine-filled plastic syringes and the findings in clinical tests are presented in this report.

Do Postcard Reminders Improve Influenza Compliance? A Prospective Trial of Different Postcard "Cues"

E.B. Larson, J. Bergman, F. Heidrich, B.L. Alvin and R. Schneeweiss. Med Care 1982 Jun;20(6):639-48.

Authors' abstract: A randomized trial of various postcard reminder "cues" was performed to improve understanding of health-related behavior and to find better strategies for improving influenza vaccination compliance. Data were gathered on 283 high-risk patients (92 percent response rate) who received: 1) a "neutral" cue simply announcing the availability of vaccine; 2) a "Health-Belief-Model" card written to take advantage of the association between certain health beliefs and vaccination behavior; 3) a "personal" card signed by the patient's physician; or 4) no postcard. The highest rate of vaccination occurred among recipients of the Health-Belief-Model postcard (51.5 percent vs. 20.2 percent for control, $p < 0.001$). Linear logistic regression analysis found that age, prior vaccination history and experimental group had a significant effect on likelihood of being vaccinated. After adjusting for age and prior vaccination experience, the vaccination rate was found to be significantly higher for persons receiving the Health-Belief-Model postcard compared with persons receiving no postcard or a neutral postcard. We conclude that reminder postcards emphasizing elements of the health belief model may help increase vaccination rates.

Expanding the Nurse's Role to Improve Preventive Service in an Outpatient Clinic

J.R. Hoey, H.P. McCallum and E.M. Lepage. Can Med Assoc J 1982 Jul 1;127(1):27-8.

Authors' abstract: To help resolve the conflicting demands of primary and secondary care in hospital medical clinics, a program was developed whereby, with the physicians' agreement, nurses would select and vaccinate clinic patients eligible for influenza vaccination. In a controlled trial the nurses offered vaccination to half of the eligible patients attending morning sessions and vaccinated 35% of them. In contrast, physicians in the afternoon sessions, who were unaware of the program, vaccinated only 2% of similar patients. These results show that, although these physicians agree with guidelines for influenza vaccination, they are not currently providing the service. The use of nursing personnel to provide this and other types of primary medical care for clinic patients is a reasonable alternative.

Pharmacist-Coordinated Pneumonia and Influenza Vaccination Program

W.J. Spruill, J.W. Cooper, and W. J. Taylor. Am J Hosp Pharm 1982 Nov;39(11):1904-6.

Authors' abstract: High-risk candidates in an ambulatory-care center were identified and immunized against pneumococcal pneumonia and influenza in a program coordinated by a pharmacist. Patients determined to be at increased risk for pneumococcal pneumonia were notified by letter of the vaccination program and encouraged to participate. Participants were then screened by their health-care providers to determine whether they were candidates for the vaccination. Those who received the pneumococcal pneumonia vaccine were later urged to be immunized against influenza virus. Of 1593 patients selected as possible vaccine candidates, 474 received the pneumococcal vaccine and 397 received the influenza vaccine. No confirmed cases of pneumococcal pneumonia and only one case of flu-like syndrome developed among the immunized patients. Income from the program exceeded its cost, excluding the salaries of the center's employees. Substantial savings were projected from reduced future treatment costs. The pharmacist had initiated and coordinated a successful effort to increase vaccine use and decrease morbidity.

Government and Law

Rubella Susceptibility in Inner-City Adolescents: The Effect of a School Immunization Law

D.B. Nelson, M.M. Layde and T.B. Chatton. Am J Public Health 1982 Jul;72(7):710-3.

Authors' abstract: In order to improve the immune status of girls in our medical clinic, we conducted a prospective sero-survey to identify susceptibles and developed a system for vaccinating non-immune girls. Over an 18-month period, 481 inner-city adolescents were screened. Susceptibility rate defined by a titer less than 1:8 was 12 percent and did not differ significantly with regard to age or race. Nine months into the study period, the State of Wisconsin enacted a "no immunization—no school" law. The susceptibility rate dropped from 22 percent prior to the enactment of the law, to 5 percent after. Of the 60 girls identified as susceptible, 54 (90 percent) kept their follow up appointments for vaccinations. Enforced state immunization laws appear to be effective in lowering rubella susceptibility.

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